



SARS-CoV-2 and COVID-19

Data and Science

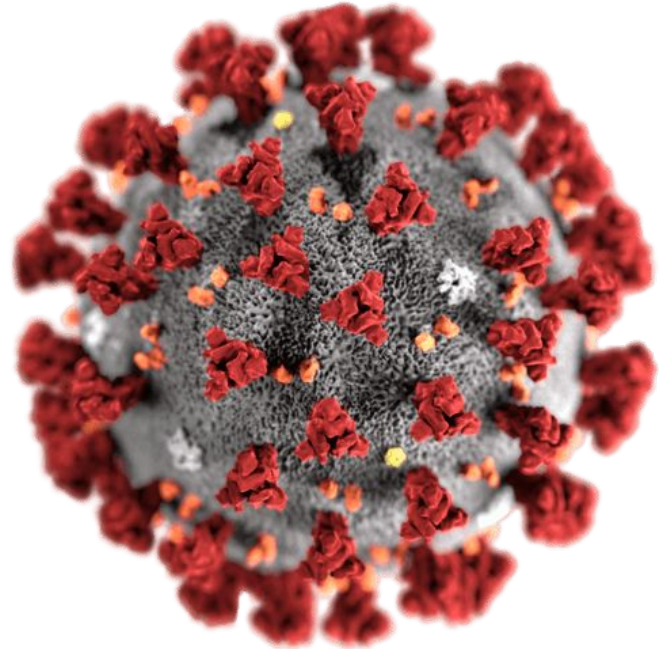
Prepared by: Jack Hidary

VISIT...

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SARS-CoV-2

- SARS-CoV-2 is a **virus** of the coronaviridae family
- It is the part of the same family of viruses that caused SARS, MERS and other diseases.
- Coronavirus Disease 2019 (COVID-19) is the **disease** caused by SARS-CoV-2, which is a respiratory infection that includes symptoms such as fever, cough, and shortness of breath.
- It is named SARS-CoV-2 due to the genetic phylogeny of the virus, not due to the course of disease/outcomes of SARS-CoV of 2003.





SARS-CoV-2

Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) officially changed the name of 2019-nCoV to **SARS-CoV-2** on March 2, 2020.

- SARS-CoV-2 originated in Wuhan and is *zoonotic*, i.e, it spread from animals to humans
- Coronaviruses are named for the crown-like spikes on their surface.

The species *Severe acute respiratory syndrome-related coronavirus*: classifying 2019-nCoV and naming it SARS-CoV-2

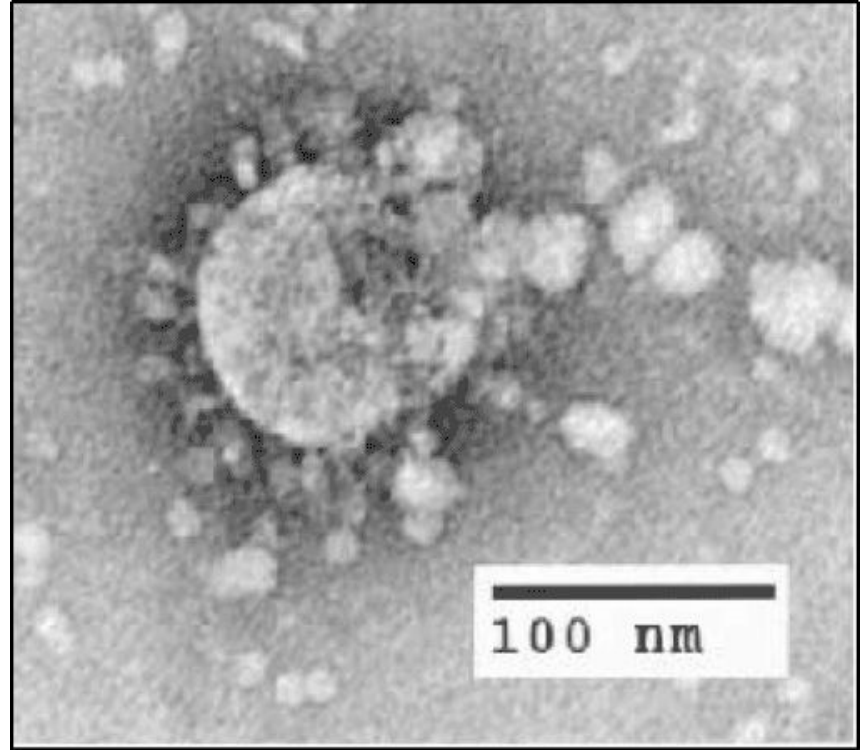
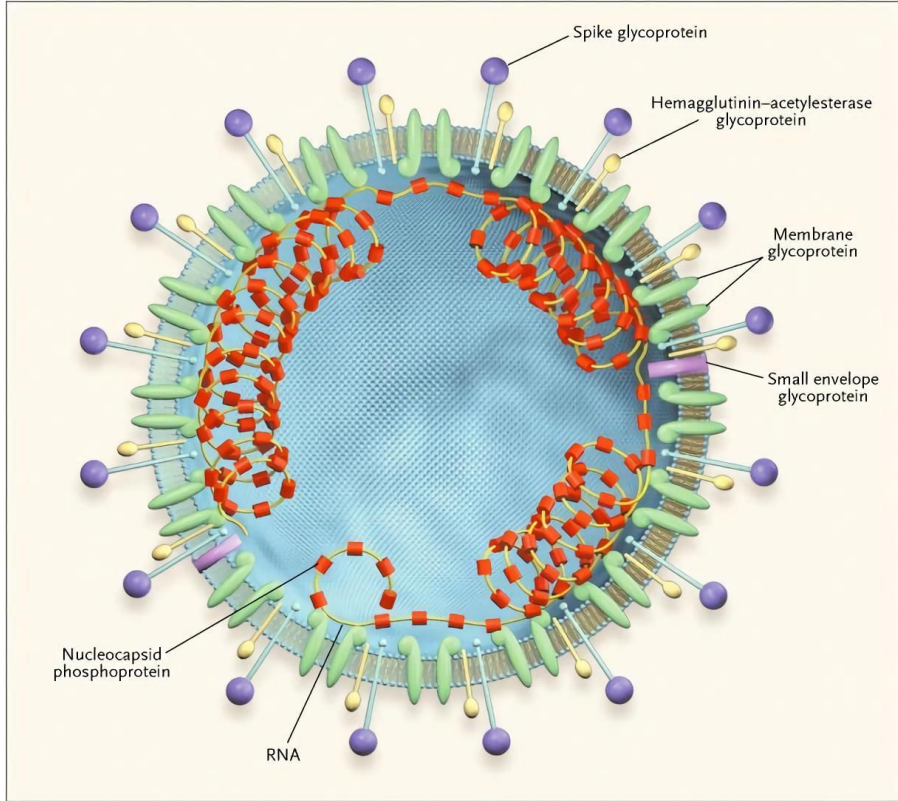
Coronaviridae Study Group of the International Committee on Taxonomy of Viruses

Nature Microbiology (2020) | [Cite this article](#)

20k Accesses | 395 Altmetric | [Metrics](#)

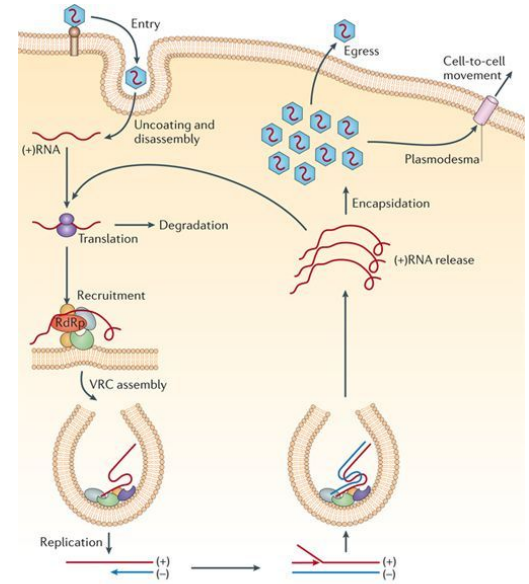
The present outbreak of a coronavirus-associated acute respiratory disease called coronavirus disease 19 (COVID-19) is the third documented spillover of an animal coronavirus to humans in only two decades that has resulted in a major epidemic. The *Coronaviridae* Study Group (CSG) of the International Committee on Taxonomy of Viruses, which is responsible for developing the classification of viruses and taxon nomenclature of the family *Coronaviridae*, has assessed the placement of the human pathogen, tentatively named 2019-nCoV, within the *Coronaviridae*. Based on phylogeny, taxonomy and established practice, the CSG recognizes this virus as forming a sister clade to the prototype human and bat severe acute respiratory syndrome coronaviruses (SARS-CoVs) of the species *Severe acute respiratory syndrome-related coronavirus*, and designates it as SARS-CoV-2. In order to facilitate communication, the CSG proposes to use the following naming convention for individual isolates: SARS-CoV-2/host/location/isolate/date. While the full spectrum of clinical manifestations associated with SARS-CoV-2 infections in humans remains to be determined, the independent zoonotic transmission of SARS-CoV and SARS-CoV-2 highlights the need for studying viruses at the species level to complement research focused on individual pathogenic viruses of immediate significance. This will improve our understanding of virus–host interactions in an ever-changing environment and enhance our preparedness for future outbreaks.

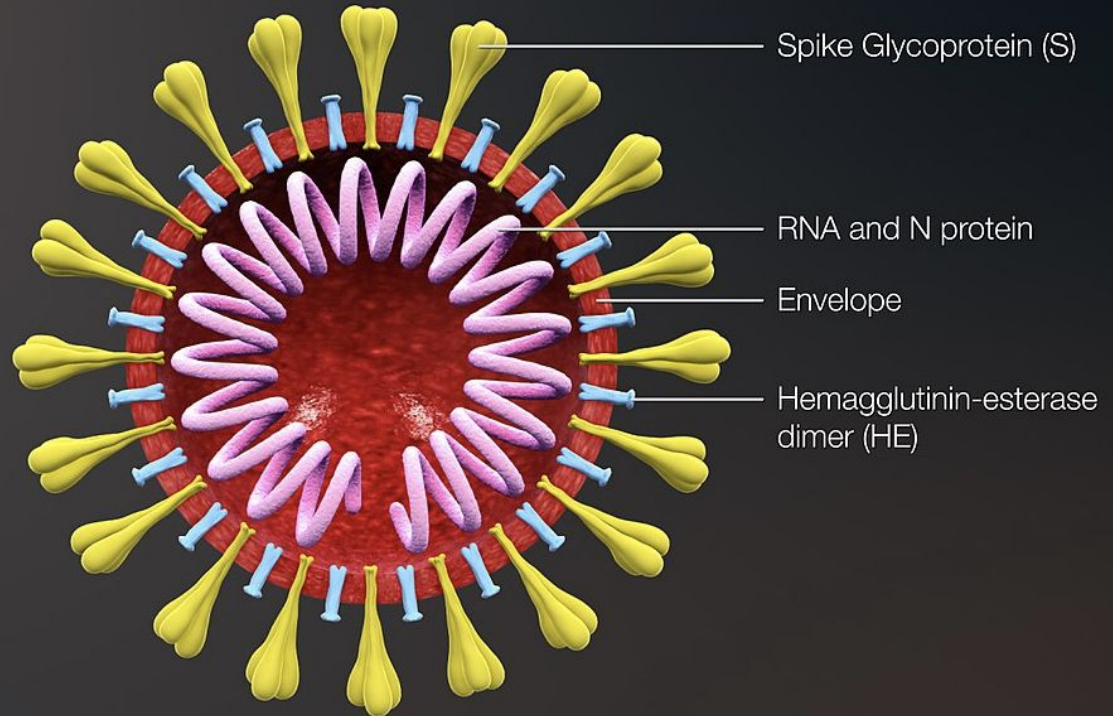
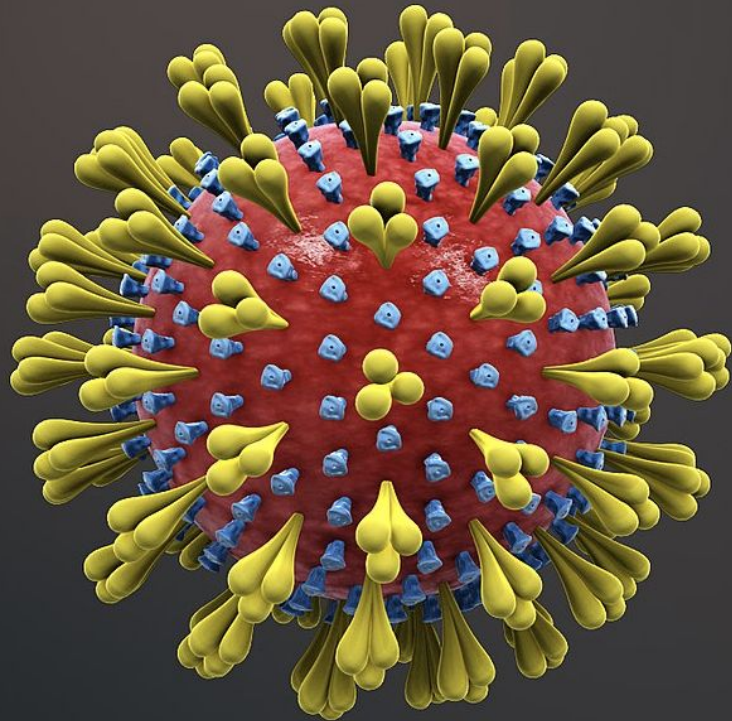
Diagram and Electron Microscope Image of SARS-CoV-2



SARS-CoV-2 is a (+)RNA Virus

- SARS-Cov-2 is a single stranded, + sense RNA virus
- This means that it skips the step of inserting nucleotides into the host DNA in order to produce mRNA (*transcription*) and jumps right to *translation* to produce proteins that it needs for its own replication.
- The viral RNA is enclosed in a capsid which, in the case of Cov-2, attaches using its surface spike glycoproteins to a receptor on the host cell. The host cell then transports the virus into the cell and the capsid is shed, exposing the RNA strand. The RNA strand can then use the host ribosomal apparatus to produce the proteins which the virus needs.
- The virus assembles a viral replication complex (VRC) inside the host cell. The VRC produces a (-)RNA complementary to the viral (+) RNA which is then used as a template to mass-replicate the (+)RNA. These copies are then encapsidated and can egress from the host cell to infect additional cells.







Coronaviridae Linnaean Classification

Severe acute respiratory syndrome-related coronavirus: The species and its viruses – a statement of the Coronavirus Study Group

 Alexander E. Gorbalenya, Susan C. Baker, Ralph S. Baric, Raoul J. de Groot, Christian Drosten, Anastasia A. Gulyaeva, Bart L. Haagmans, Chris Lauber, Andrey M. Leontovich, Benjamin W. Neuman, Dmitry Penzar, Stanley Perlman, Leo L.M. Poon, Dmitry Samborskiy, Igor A. Sidorov, Isabel Sola, John Ziebuhr

doi: <https://doi.org/10.1101/2020.02.07.937862>

This article is a preprint and has not been certified by peer review [what does this mean?].

Abstract

Full Text

Info/History

Metrics

 Preview PDF

Category	Virus
Realm	<i>Riboviria</i>
Order	<i>Nidovirales</i>
Suborder	<i>Cornidovirineae</i>
Family	<i>Coronaviridae</i>
Subfamily	<i>Coronavirinae</i>
Genus	<i>Betacoronavirus</i>
Subgenus	<i>Sarbecovirus</i>
Species	<i>Severe acute respiratory syndrome-related coronavirus</i>
Individuum	SARS-CoV SARS-CoV_PC4-227 SARSr-CoV_BtKY72 SARS-CoV-2/X1/Human/2019/Wuhan_XYZ12345



Human Coronavirus Types

Coronaviruses are named for the crown-like spikes on their surface. There are four main genus sub-groupings of coronaviruses, known as alpha, beta, gamma, and delta.

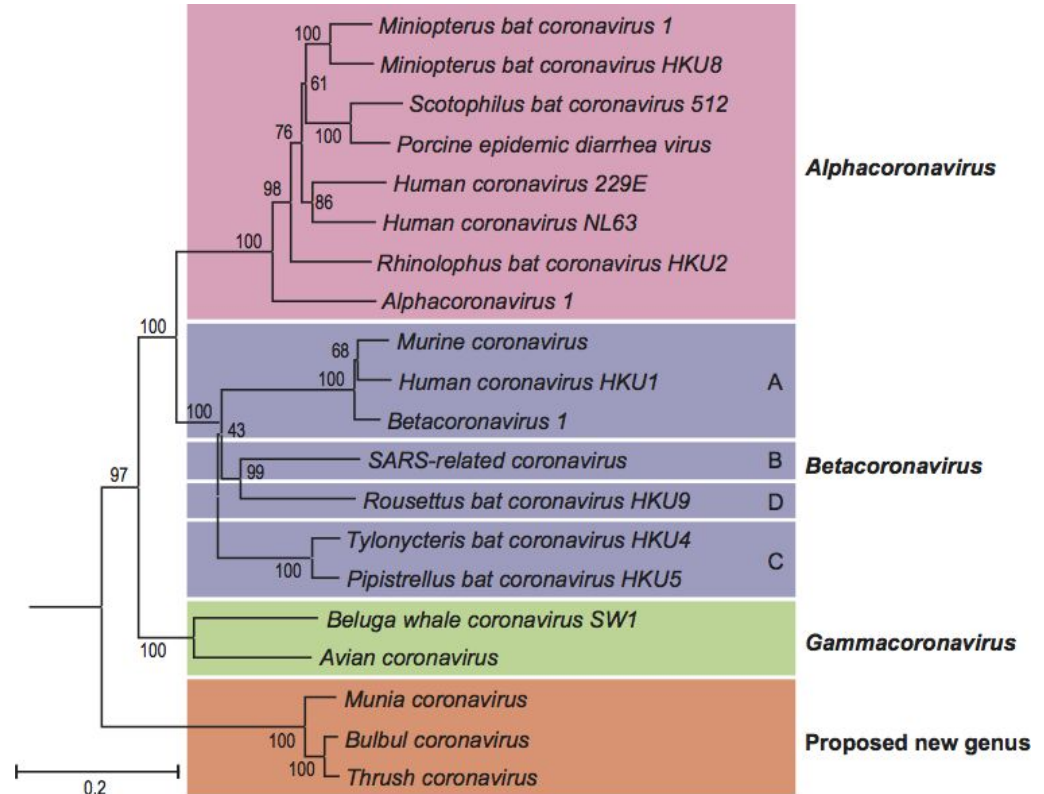
Human coronaviruses were first identified in the mid-1960s. The seven coronaviruses that can infect people are:

1. 229E (alphacoronavirus)
2. NL63 (alphacoronavirus)
3. OC43 (betacoronavirus)
4. HKU1 (betacoronavirus)
5. MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS)
6. SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS)
7. [SARS-CoV-2 \(the novel betacoronavirus that causes coronavirus disease 2019, or COVID-19\)](#)

Betacoronavirus

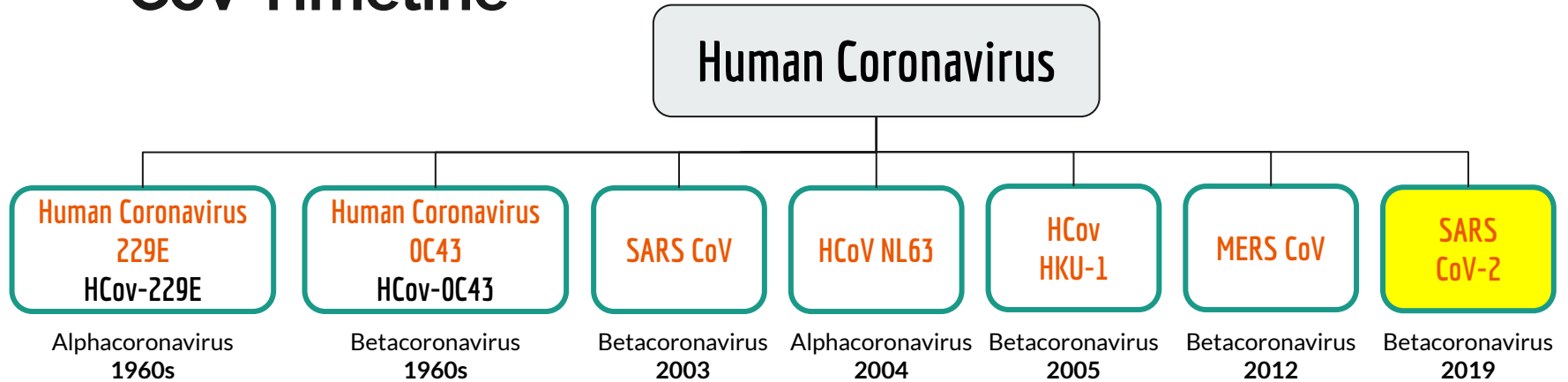
SARS-CoV-2 is part of the coronavirus family and of genus *betacoronavirus*.

The coronavirus that hit Hong Kong in 2005 and the SARS-CoV that hit Asia in 2003 were also of the *betacoronavirus* genus.





CoV Timeline





Disease Spread Terms

- **Endemic:** refers to the constant presence and/or usual prevalence of a disease in a geographic population
- **Outbreak:** carries the same definition as an epidemic but is often used to describe a more limited geographic event.
- **Epidemic:** refers to a sudden increase in the number of cases of a disease above what is normally expected
- **Pandemic:** refers to an epidemic that has spread over several countries or continents, usually affecting a large number of people

Quarantine vs. Isolation

Quarantine

- To separate and restrict the movement of well persons who may have been exposed to a communicable disease
- Monitor to see if they become ill
- These people may have been exposed to a disease and do not know it, or they may have the disease but do not show symptoms.
- Quarantine can also help limit the spread of communicable disease.

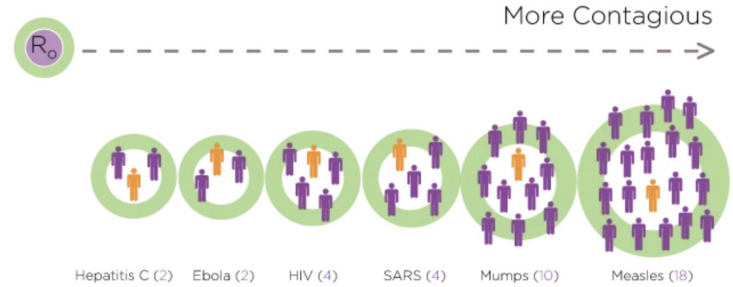
Isolation

- To separate ill persons who have a communicable disease from those who do not have that disease
- Restricts the movement of ill persons to help stop the spread of certain diseases
- Example: Isolation for patients with infectious tuberculosis

Ro

How contagious is a disease?

Scientists use "R naught," or R_0 , to estimate how many other people one sick person is likely to infect



R_0 (R-naught) is the avg number of people which an infected person infects:

- If R_0 is less than 1, each existing infection causes less than one new infection. In this case, the disease will decline and eventually die out.
- If R_0 equals 1, each existing infection causes one new infection. The disease will stay alive and stable, but there won't be an outbreak or an epidemic.
- If R_0 is more than 1, each existing infection causes more than one new infection. The disease will spread between people, and there may be an outbreak or epidemic.

R_0 assumes:

- no one has been vaccinated
- no one has had the disease before
- there's no way to control the spread of the disease



These numbers are projected by Dr. James Lawler, MD of UNMC, a noted infectious diseases expert, for the American Hospital Association (AHA).

According to Dr. Lawler, the projections in this slide could be reduced and spread over a longer period of time (thus allowing for resources to catch up) if governments and communities take aggressive measures as seen in Singapore, etc. See [NPI measures](#).

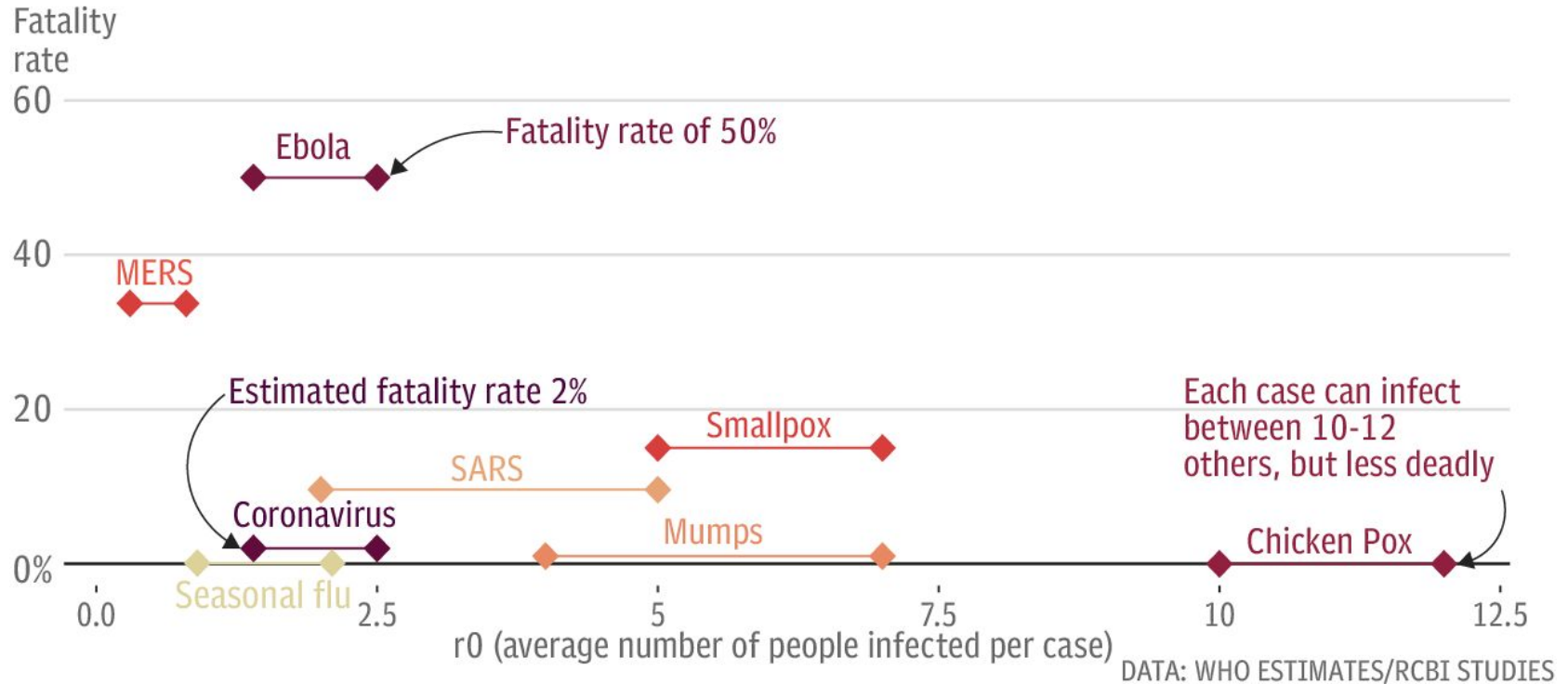
Best Guess Epidemiology

- $R_0 = 2.5$; Doubling time 7-10 days
 - Community attack rate = 30-40%
 - Cases requiring hospitalization = 5%
 - Cases requiring ICU care = 1-2%
 - Cases requiring ventilatory support = 1%
 - CFR = 0.5%
- Community epi wave 2 months
- US: 96 million cases
- US: 4.8 million admissions
- US: 1.9 million ICU
- US: 1 million PPV
- US: 480,000 deaths
- PREPARE FOR DISEASE BURDEN ROUGHLY 10X SEVERE FLU SEASON**



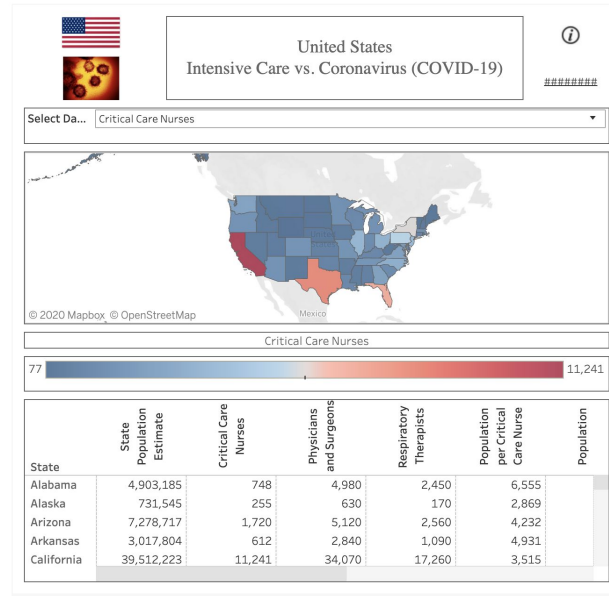
Coronavirus: How does it compare to other diseases?

Average reproductive rate (r_0) of infectious diseases and fatality rate



ICU beds available vs. Rise in Demand

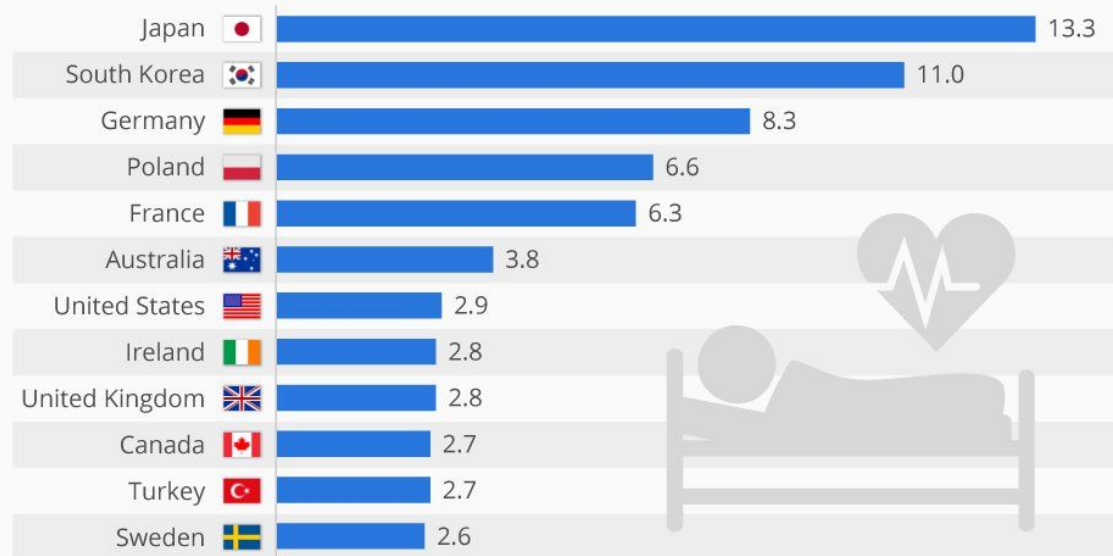
- Will there be sufficient ICU resources for the number of serious COVID-19 cases ?
- State-by-state data available at the link in the notes.



Assessing Capacity

The Countries With The Most Hospital Beds

Total hospital beds per 1,000 of the population in selected countries*



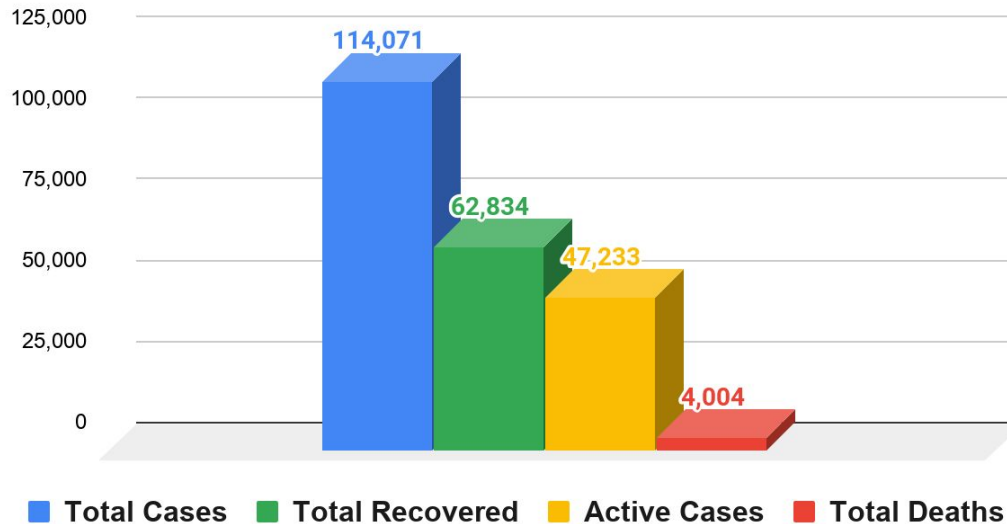


Spread of SARS-CoV-2



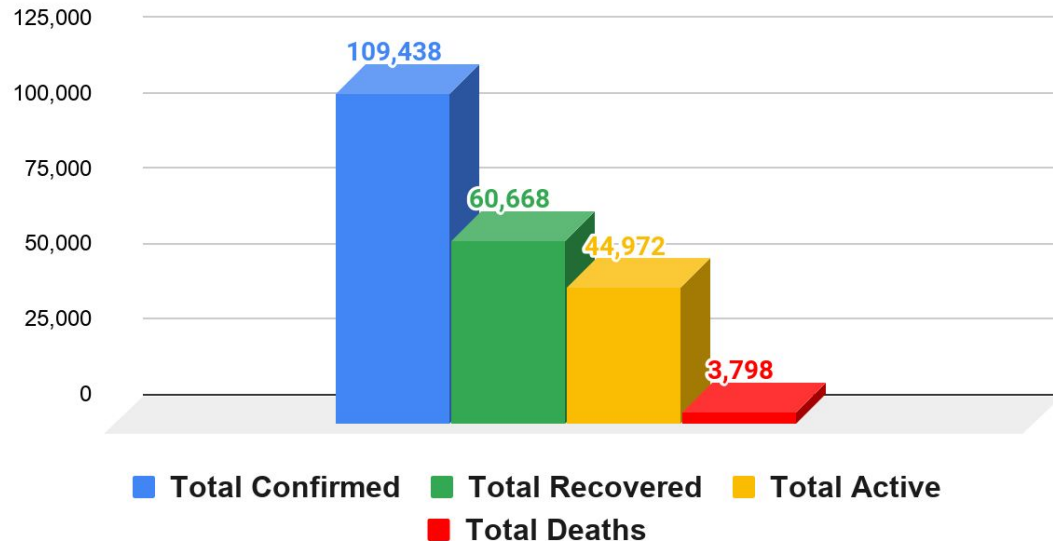
Real-Time Statistics on COVID-19 - Worldometers

Worldometers COVID-19 Data



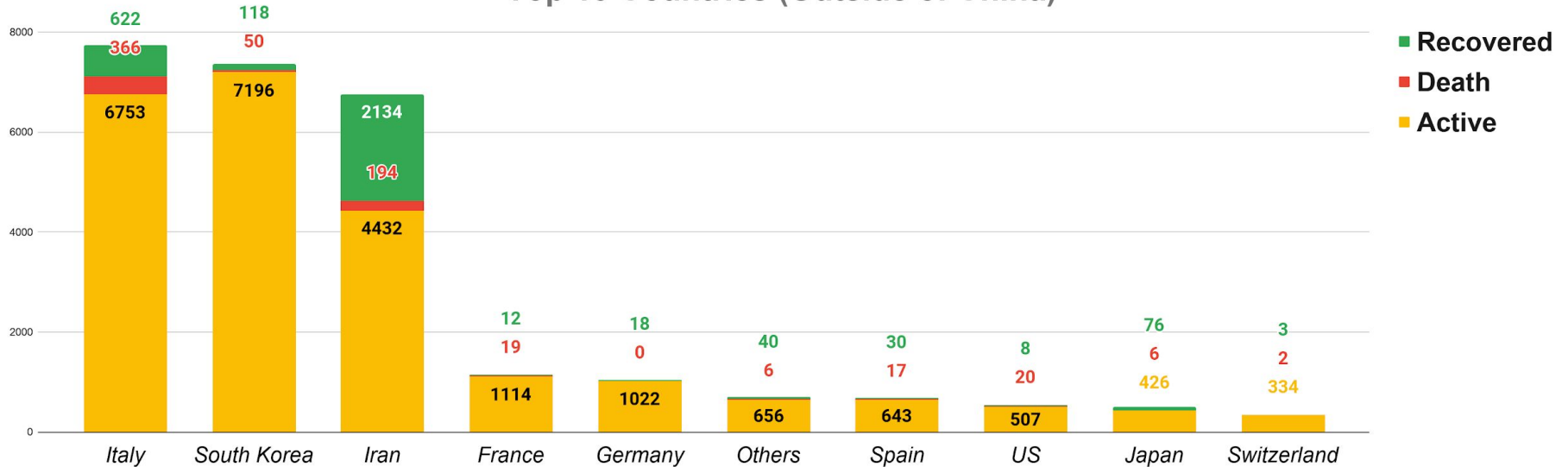
Real-Time Statistics on COVID-19 - John Hopkins

Johns Hopkins COVID-19 Data



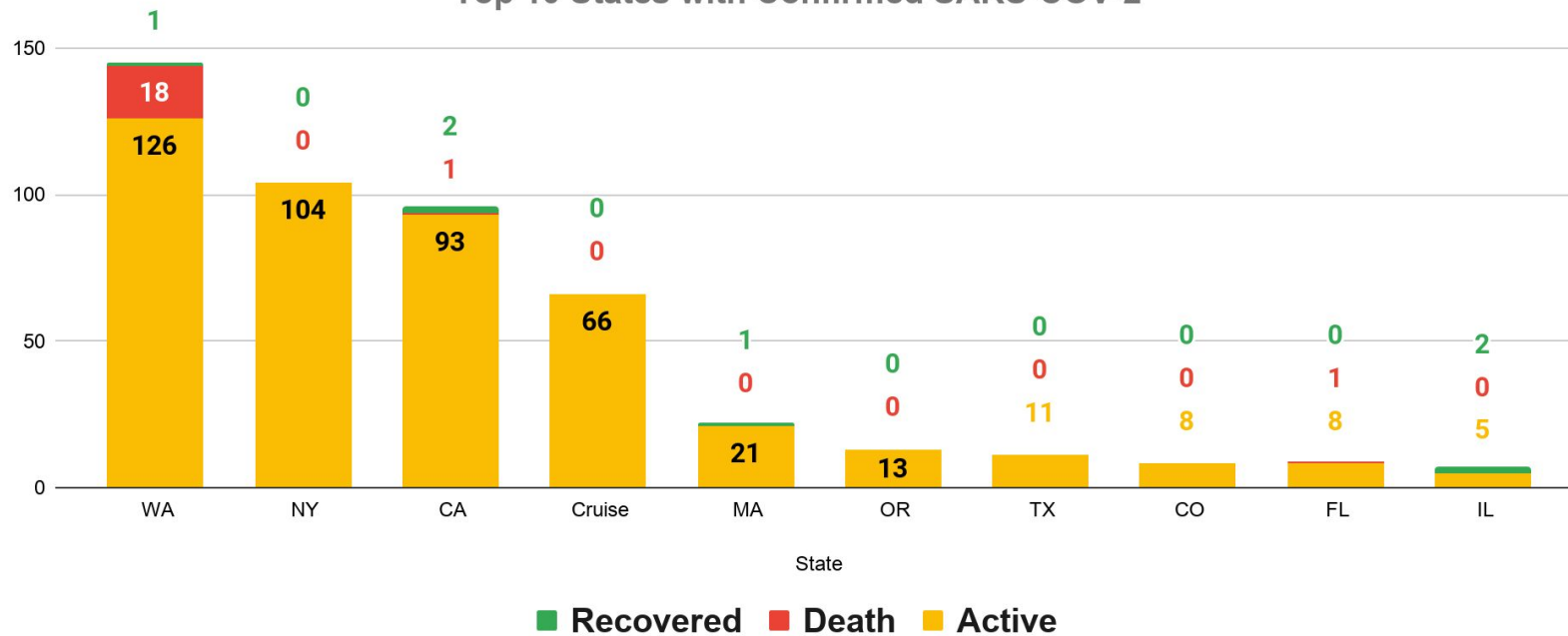
Top 10 Countries outside of China

Top 10 Countries (Outside of China)



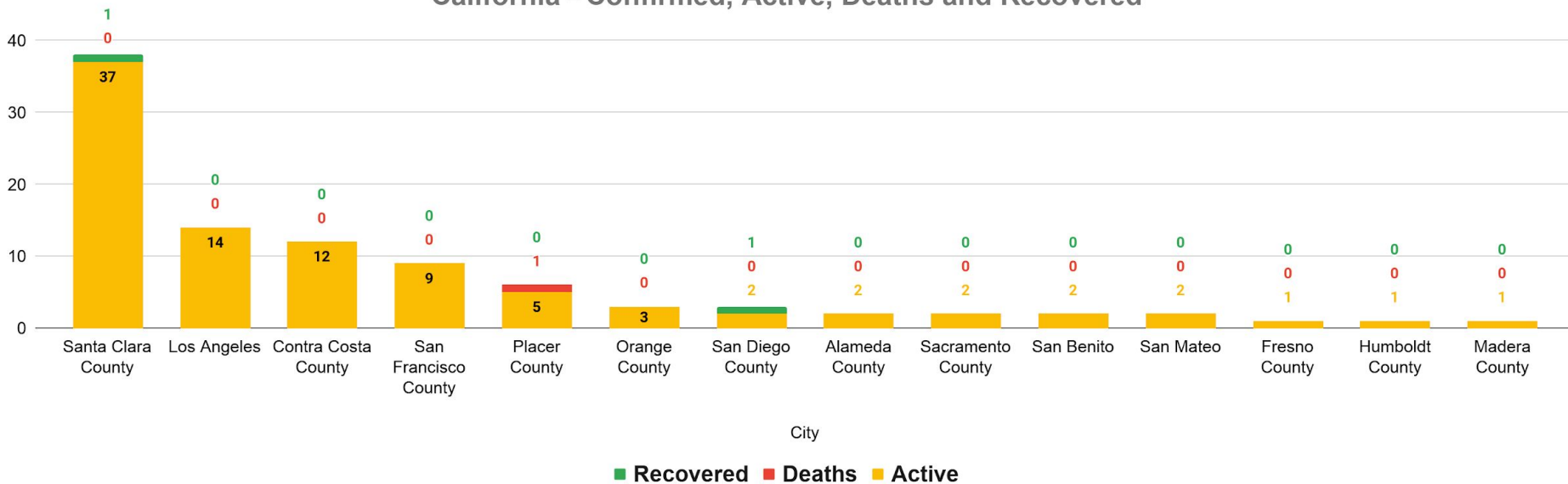
USA

Top 10 States with Confirmed SARS-COV-2



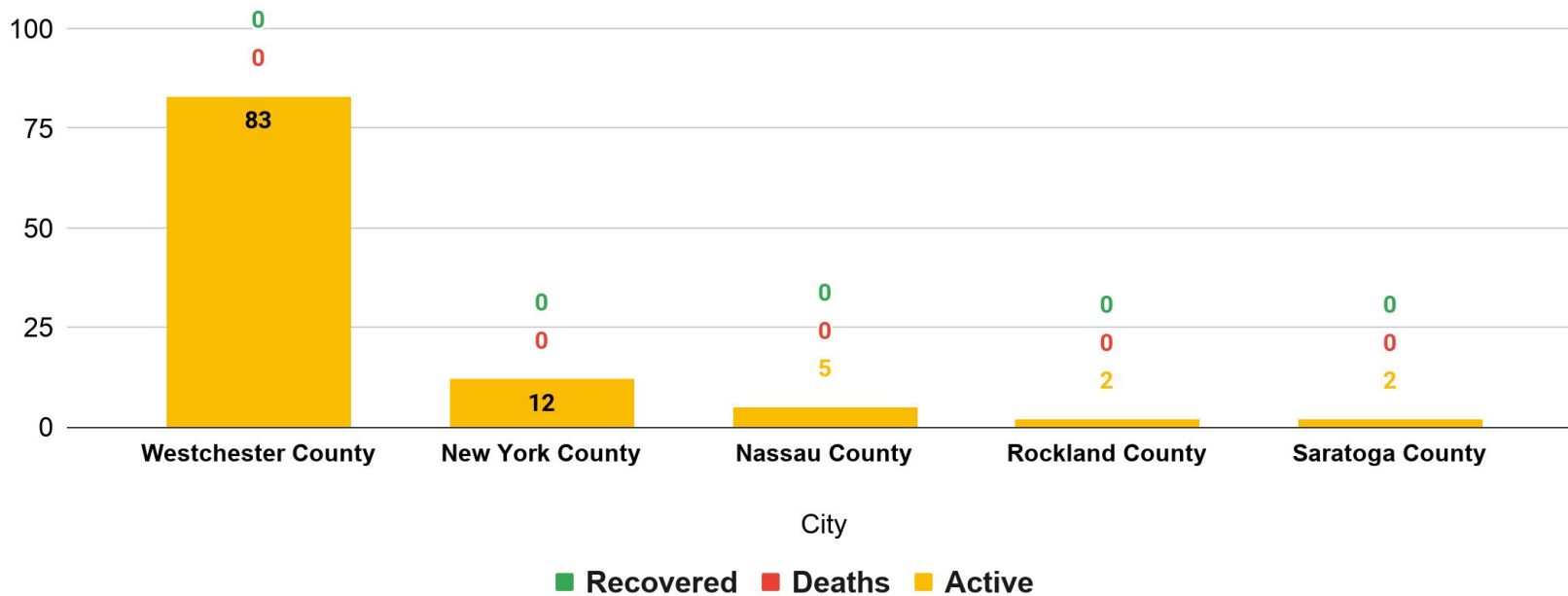
CA

California - Confirmed, Active, Deaths and Recovered



NY

NY - Confirmed, Active, Deaths and Recovered



COVID-19 CFR by Age Distribution

Figure 1: COVID-19 Fatality rates by age

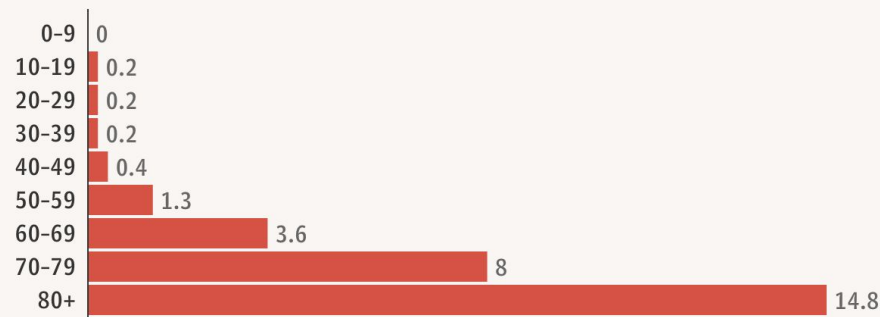
Age	Fatality rate* (%)
80+ years old	14.8
70-79 years old	8.0
60-69 years old	3.6
50-59 years old	1.3
40-49 years old	0.4
30-39 years old	0.2
20-29 years old	0.2
10-19 years old	0.2
0-9 years old	No fatalities

Source: China CDC.

Analysis based on cases diagnosed as of 2/17/2020.

*Fatality rate = (Number of deaths / Number of cases) = probability of dying if infected by the virus (%).

Coronavirus fatality rate
% of deaths within each age-range



WORLDOMETERS.INFO

Note: Age is a factor primarily due to *comorbidity* with other diseases. See comorbidity chart in this deck. Older individuals tend to have these pre-existing conditions.



China Data on Comorbidity

COVID-19 Fatality Rate by COMORBIDITY:

PRE-EXISTING CONDITION	DEATH RATE
Cardiovascular disease	10.5%
Diabetes	7.3%
Chronic respiratory disease	6.3%
Hypertension	6.0%
Cancer	5.6%
<i>no pre-existing conditions</i>	0.9%

NPI - how to slow down the outbreak

https://www.paho.org/disasters/index.php?option=com_docman&view=dwnload&category_slug=tools&alias=530-pandinflu-leadershipduring-tool-4&Itemid=1179&lang=en

HEALTH

TOOL
4

NON-PHARMACEUTICAL
INTERVENTIONS (NPIs):
ACTIONS TO LIMIT THE SPREAD OF THE
PANDEMIC IN YOUR MUNICIPALITY


PREPAREDNESS


RESPONSE

This tool will help you to:

- Understand non-pharmaceutical interventions (NPIs)
- Use these as strategies to limit the spread of a severe pandemic from person to person
- Learn when and how to implement NPIs in order to reduce deaths

Who will implement this tool:

The health sector will be responsible for advising the mayor and the municipal team on how

WHAT ARE NON-PHARMACEUTICAL INTERVENTIONS?

During a severe pandemic, there are different approaches to limiting the spread of the illness. Pharmaceutical (drug) interventions, such as vaccines and anti-viral medications to prevent the disease or its complications *may not* be available in many areas of the world in sufficient quantities to make a significant contribution toward reducing deaths.

NPIs include both actions that individuals and households can take (e.g. frequent hand washing, covering coughs and sneezes, and keeping a distance from sick people) and *social distancing policies* that communities can enact (e.g. closing schools, working from home, restricting public gatherings) that are specifically geared to limiting the spread of a disease that is transmitted from person to person.

NPIs are the most important tool that mayors and municipal leadership teams will have to reduce deaths. Not only will they be available and accessible at the local level, but they are likely to be very effective in limiting the spread of the disease, and reducing the number of deaths. The *Crisis and Emergency Risk Communication* section, Tools 12–14, will give you ideas on how to communicate interventions to the public.



NPI - how to slow down the outbreak

https://www.paho.org/disasters/index.php?option=com_docman&view=download&category_slug=tools&alias=530-pandinflu-leadershipduring-tool-4&Itemid=1179&lang=en

Close schools and childcare facilities

Why: Influenza can easily travel through childcare facilities and schools because children tend to spread germs more rapidly than adults. Closing schools and childcare facilities protects children by decreasing the spread of the disease among them, and also dramatically decreases the risk of children bringing the disease home or infecting other members of the community.

Instructions: Depending on the severity of the pandemic, authorized government officials may need to close schools and childcare facilities to limit the spread of the disease.

Requirements for success:

- Depending on the situation in your country, the central government may make the decision about whether or not to close schools, or they may leave it up to the local areas. Refer to your national and district plans, if available, and develop your plans to include both possibilities.
- The consistent implementation of closings among all schools in the municipality
- Providing families with alternative options for their children's education



SARS-Cov-2 has mutated into two major strains

- L-type
- S-type
- The difference is in a protein called “Spike” which is the main vaccine target



Genomic Lineage of SARS-CoV-2

RESEARCH ARTICLE MICROBIOLOGY

On the origin and continuing evolution of SARS-CoV-2

Xiaolu Tang^{1,7}, Changcheng Wu^{1,7}, Xiang Li^{2,3,4,7}, Yuhe Song^{2,5,7}, Xinmin Yao¹, Xinkai Wu¹, Yuange Duan¹, Hong Zhang¹, Yirong Wang¹, Zhaohui Qian⁶, Jie Cui^{2,3,*}, and Jian Lu^{1,*}

1. State Key Laboratory of Protein and Plant Gene Research, Center for Bioinformatics, School of Life Sciences, Peking University, Beijing, 100871, China
2. CAS Key Laboratory of Molecular Virology & Immunology, Institut Pasteur of Shanghai, Chinese Academy of Sciences, China
3. Center for Biosafety Mega-Science, Chinese Academy of Sciences, China
4. University of Chinese Academy of Sciences, China
5. School of Life Sciences, Shanghai University, China
6. NHC Key Laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing
7. These authors contributed equally to this work.

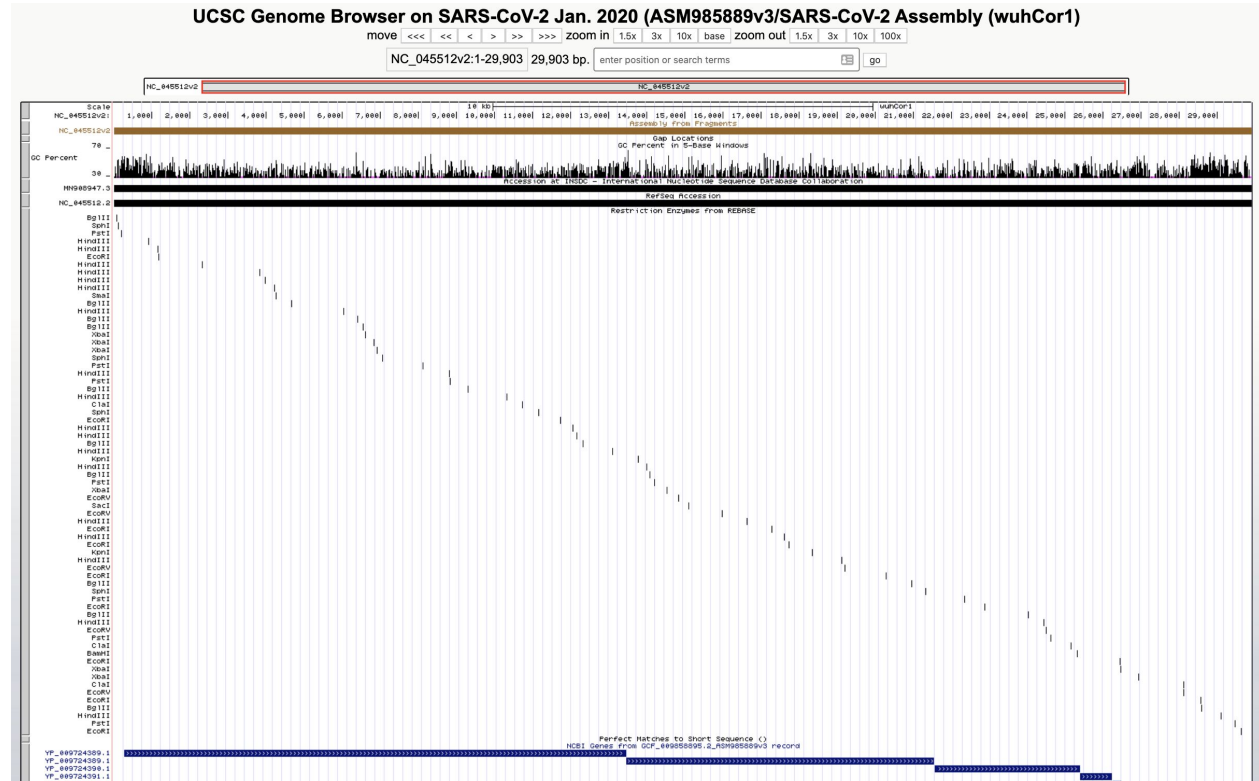
*Corresponding authors:

Jian Lu, Email: LUJ@pku.edu.cn

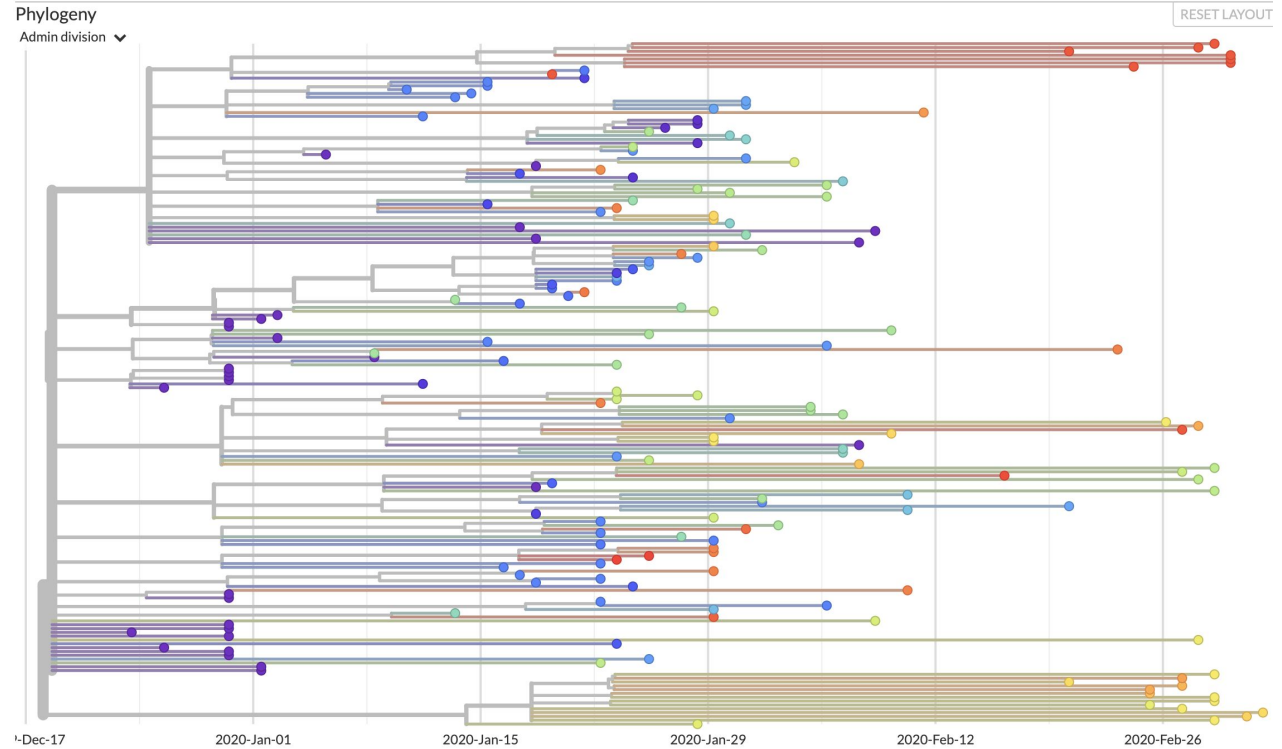
Jie Cui, Email: jcui@ips.ac.cn

Genomic Sequence of SARS-CoV-2

The genomic sequence of SARS-CoV-2 is long compared with other viruses: approximately 26,000 to 32,000 bases or RNA nucleotides



Phylogeny of SARS-CoV-2





The genome annotation of 2019-nCoV strain IVDC-HB-01/2019 (EPI_ISL_402119 in GISAID)

Gene name	Coding region (nt)	Protein length (aa)
orf1a	266-13483	4405
orf1ab	266-13468, 13468- 21555	7096
S	21563 - 25384	1273
3a	25393 - 26220	275
3b	25814-25882	22
	26183-26281	32
E (envelope protei)	26245-26472	75
M (matrix protein)	26523- 27191	222
p6	27202:27387	61
7a	27394- 27759	121
7b	27756:27887	43
8b	27894 - 28259	121
9b	28284-28577	97
N(nucleocapsid)	28274 - 29533	419
orf14	28734-28955	73



SARS-Cov-2 Genome Sequence

Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome

GenBank: MN908947.3

[FASTA](#) [Graphics](#)

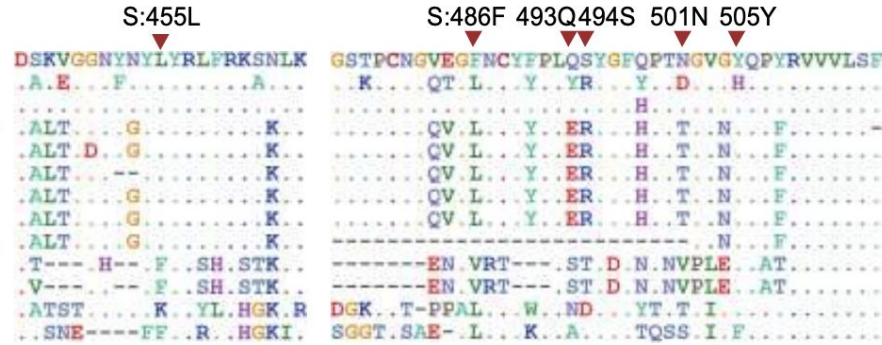
[Go to:](#) ☐

LOCUS	MN908947	29903 bp ss-RNA	linear	VRL 11-FEB-2020
DEFINITION	Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome.			
ACCESSION	MN908947			
VERSION	MN908947.3			
KEYWORDS	.			
SOURCE	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)			
ORGANISM	Severe acute respiratory syndrome coronavirus 2 Viruses; Riboviria; Nidovirales; Coronavirineae; Coronaviridae; Orthocoronavirinae; Betacoronavirus; Sarbecovirus.			

Molecular divergence and selective pressures during the evolution of SARS-CoV-2 and related viruses.

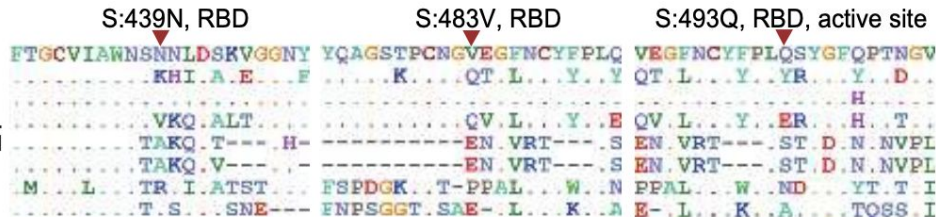
B

SARS-CoV-2
Bat RaTG13
GD Pangolin-CoV
GX Pangolin-CoV_P2V
GX Pangolin-CoV_P5E
GX Pangolin-CoV_P1E
GX Pangolin-CoV_P5L
GX Pangolin-CoV_P4L
GX Pangolin-CoV_P3B
Bat SARSr-CoV_ZXC21
Bat SARSr-CoV_ZC45
SARS-CoV
Bat SARSr-BM48-31

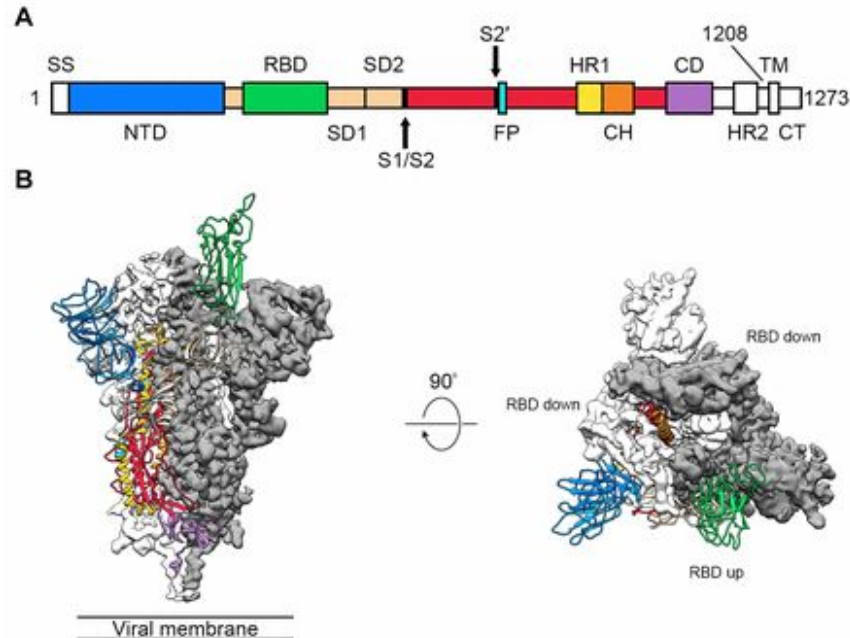


C

SARS-CoV-2
Bat RaTG13
GD Pangolin-CoV
GX Pangolin-CoV_P5L
Bat SARSr-CoV_ZXC21
Bat SARSr-CoV_ZC45
SARS-CoV
Bat SARSr-BM48-31



SARS-CoV-2-S spike protein



Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation

Daniel Wrapp^{1,*}, Nianshuang Wang^{1,*}, Kizzmekia S. Corbett², Jory A. Goldsmith¹, Ching-Lin Hsieh¹, Olubukola Abiona², Barney S. Graham², Jason S. McLellan^{1,†}

¹Department of Molecular Biosciences, The University of Texas at Austin, Austin, TX 78712, USA.

²Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

†*Corresponding author. Email: jmclellan@austin.utexas.edu

* These authors contributed equally to this work.

- Hide authors and affiliations

Science 19 Feb 2020:

eabb2507

DOI: 10.1126/science.abb2507

Structure Summary

3D View

Annotations

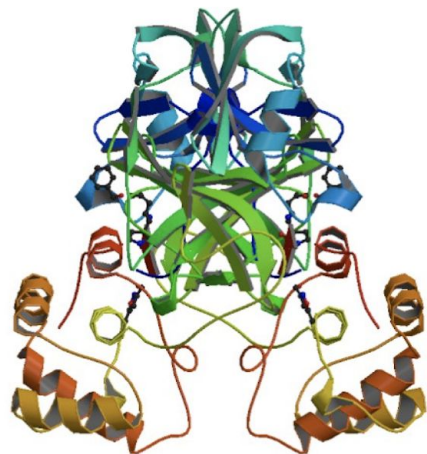
Sequence

Sequence Similarity

Structure Similarity

Experiment

< Biological Assembly 1 ? >



3D View: [Structure](#) | [Electron Density](#)

Standalone Viewers

[Protein Workshop](#) | [Ligand Explorer](#)

6LU7

The crystal structure of COVID-19 main protease in complex with an inhibitor N3

DOI: [10.2210/pdb6LU7/pdb](https://doi.org/10.2210/pdb6LU7/pdb)

Classification: [VIRAL PROTEIN](#)

Expression System: [Escherichia coli BL21\(DE3\)](#)

Deposited: 2020-01-26 Released: 2020-02-05

Deposition Author(s): [Liu, X.](#), [Zhang, B.](#), [Jin, Z.](#), [Yang, H.](#), [Rao, Z.](#)

Display Files ▾

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Experimental Data Snapshot

Method: X-RAY DIFFRACTION

Resolution: 2.16 Å

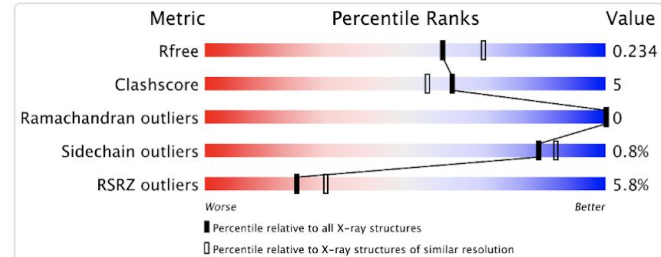
R-Value Free: 0.235

R-Value Work: 0.202

wwPDB Validation

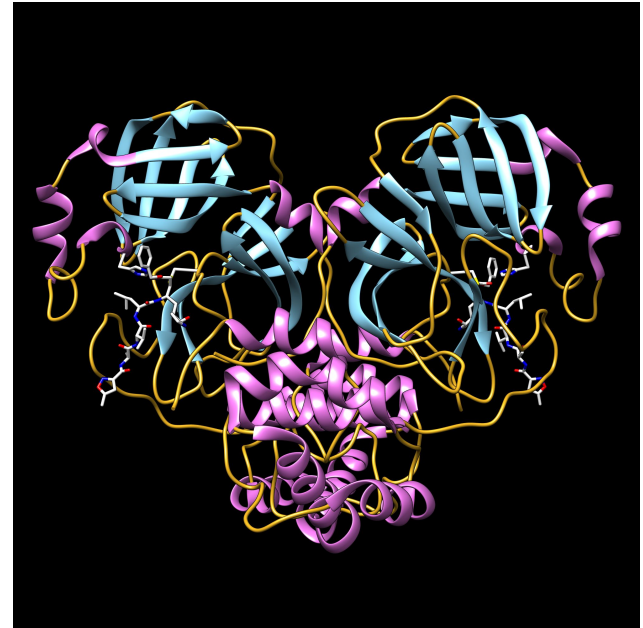
3D Report

Full Report



SARS-CoV-2 Protein

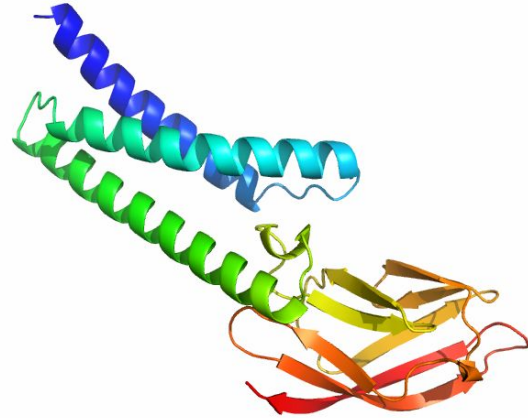
SARS-CoV-2 main protease protein with inhibitor N3 (white stick representation) covalently bound to residue cysteine 145 in the protease active site. Display shows secondary structure (helices in magenta, strands in cyan, loops in yellow). Adjacent active site residue histidine 41 is also shown.





SARS-CoV-2 Proteins

- DeepMind used their Alphafold program to predict the structure of a key protein found in SARS-Cov-2.



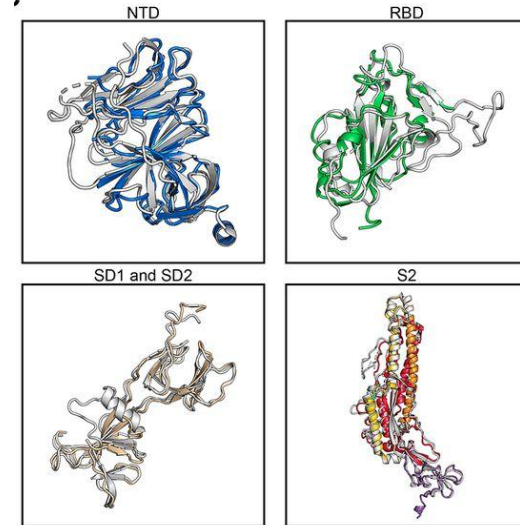
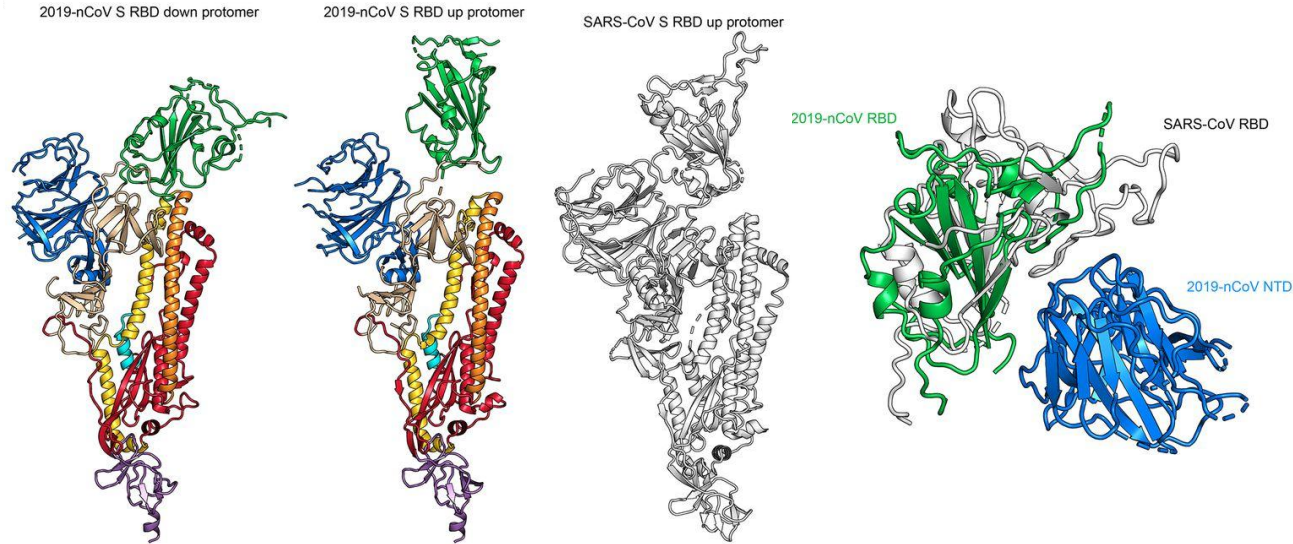


Non-structural proteins of CoV

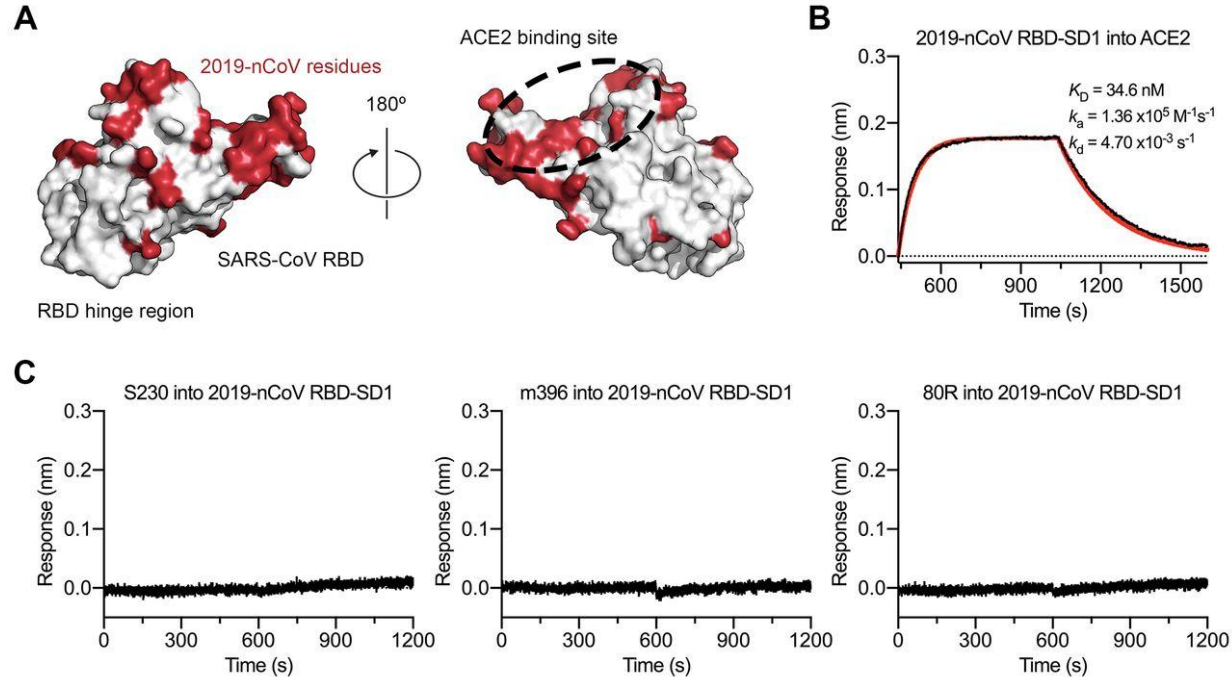
Table 1. The 16 nonstructural proteins of coronaviruses and their functions

nsp	Functions	References
nsp1	Cellular mRNA degradation, inhibiting IFN signaling	15, 16
nsp2	Unknown	17, 18
nsp3	PLP, polypeptides cleaving, blocking host innate immune response, promoting cytokine expression	19, 20
nsp4	DMV formation	21, 22
nsp5	3CL ^{Pro} , M ^{Pro} , polypeptides cleaving, inhibiting IFN signaling	23-25
nsp6	Restricting autophagosome expansion, DMV formation	26, 27
nsp7	Cofactor with nsp8 and nsp12	28, 29
nsp8	Cofactor with nsp7 and nsp12, primase	28-30
nsp9	Dimerization and RNA binding	31, 32
nsp10	Scaffold protein for nsp14 and nsp16	33-36
nsp11	Unknown	37
nsp12	Primer dependent RdRp	28, 38, 39
nsp13	RNA helicase, 5' triphosphatase	40-42
nsp14	Exoribonuclease, N7-MTase	12, 43-45
nsp15	Endoribonuclease, evasion of dsRNA sensors	46-48
nsp16	2'-O-MTase; avoiding MDA5 recognition, negatively regulating innate immunity	34, 35, 49

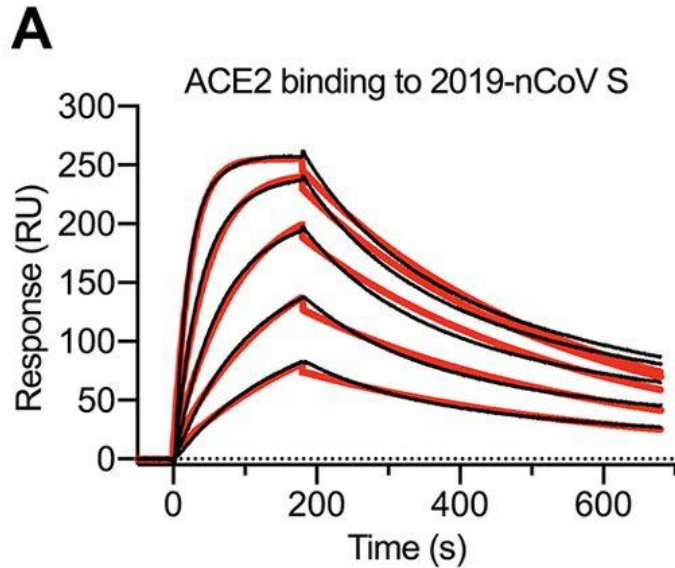
Comparison between SARS-CoV and SARS-CoV-2



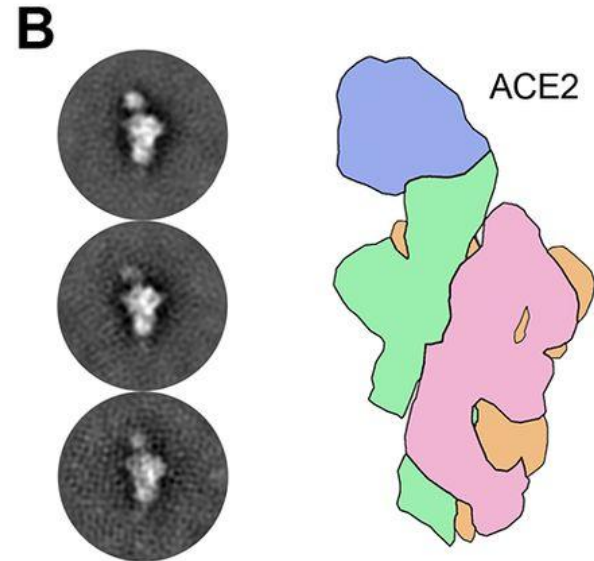
Antigenicity of the 2019-nCoV RBD



SARS-Cov-2 S binds human ACE2 with high affinity



$$K_D = 14.7 \text{ nM}$$
$$k_a = 1.88 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$$
$$k_d = 2.76 \times 10^{-3} \text{ s}^{-1}$$





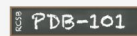
PDB



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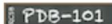
News

News by Year: [2020](#) [2019](#) [2018](#) [2017](#) [2016](#) [2015](#) [2014](#) [2013](#) [2012](#) [2011](#) [2010](#) [2009](#) [2008](#) [2007](#)

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COVID-19 Coronavirus Resources

02/06 

PDB data and related resources provide a starting point for structure-guided drug discovery and understanding of COVID-19.

- [PDB structure 6lu7](#): first high-resolution crystal structure of COVID-19 coronavirus 3CL hydrolase (Mpro) determined by Zihe Rao and Haitao Yang's research team at ShanghaiTech University (released February 5, 2020). doi: [10.2210/pdb6lu7/pdb](https://doi.org/10.2210/pdb6lu7/pdb)
- [wwPDB overview](#), including summary data for closely-related PDB structures (96% sequence identity; [CSV](#)) and other closely related SARS proteins, including a second viral protease, the RNA polymerase, the viral spike protein, a viral RNA, and other proteins ([CSV](#))
- [Molecule of the Month](#) feature on [Coronavirus Proteases](#)
- [Coronavirus painting](#)

Currently 60+ clinical trials related to SARS-CoV-2

- Most of the trials are in China

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting NEW	The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection	• Coronavirus Infections	• Drug: Lopinavir and Ritonavir Tablets • Drug: Arbidol	• Guangzhou Eighth P Hospital Guangzhou, Guangdong, China
2	☐	Recruiting NEW	Clinical Features of Suspected and Confirmed Patients of 2019 Novel Coronavirus Infection	• Coronavirus	• Other: Comprehensive treatment	• The Third Affiliated H Sun Yat-sen University Guangzhou, Guangdong, China
3	☐	Not yet recruiting NEW	A New Screening Strategy for 2019 Novel Coronavirus Infection	• Novel Coronavirus Infection Pneumonia	• Diagnostic Test: Standard screening strategy • Diagnostic Test: New screening strategy	• the Fifth Medical Center Chinese PLA General Hospital Beijing, Beijing, China
4	☐	Recruiting NEW	Detection of 2019 Novel Coronavirus in Multiple Organ System and Its Relationship With Clinical Manifestations	• Coronavirus		• The Third Affiliated H Sun Yat-sen University Guangzhou, Guangdong, China
5	☐	Not yet recruiting NEW	Humanistic Care in Patients With Coronavirus Disease 2019	• Coronavirus Disease 2019	• Behavioral: Psychological and physical rehabilitation based humanistic care	
6	☐	Recruiting NEW	Viral Excretion in Contact Subjects at High/Moderate Risk of Coronavirus 2019-nCoV Infection	• Coronavirus	• Biological: 2019-nCoV PCR	• CIC 1425 Paris, France
7	☐	Not yet recruiting NEW	Humanistic Care in Healthcare Workers in Coronavirus Disease 2019	• Coronavirus Disease 2019	• Behavioral: Humanistic Care	
8	☐	Not yet recruiting NEW	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	• Coronavirus	• Biological: MSCs-derived exosomes	



Vaccines in Development

Moderna

GlaxoSmithKline (GSK)

CureVac

J&J

Sanofi

Vir Biotech-WuXi

Moderna

- Working on a vaccine (mRNA-1273)
- Uses its mRNA (messenger ribonucleic acid) platform
 - Which tries to make drugs that direct cells in the body to make proteins to prevent or fight disease
 - Makes use of mRNA
- Plans to begin trials on 45 people in April

moderna®





CureVac

- mRNA based vaccine
- Backed by DARPA and the Melissa and Bill Gates Foundation
- Working with CEPI on a mobile mRNA manufacturing technology



GlaxoSmithKline (GSK)



- GSK has proprietary [adjuvants](#)
 - Compounds that enhance the effectiveness of vaccines
 - Can Reduce the amount of vaccine required per-dose
 - Can make more vaccine doses
- GSK is not working on their own vaccine
- GSK is offering its adjuvants to other companies in collaboration with Coalition for Epidemic Preparedness Innovations (CEPI)
 - Clover Biopharmaceuticals
 - “At Clover we look forward to evaluating the combination of GSK’s pandemic adjuvant system and our S-Trimer as a vaccine candidate. Utilizing our proprietary Timer-Tag® technology that has been shown to be recognized by antibodies produced by multiple previously-infected coronavirus patients, S-Trimer is being rapidly developed to support global efforts in combating this current and any future coronavirus outbreaks”
 - University of Queensland

PHARMACEUTICAL
BUSINESS REVIEW

25 FEB 2020

DRUG DISCOVERY

RESEARCH & DEVELOPMENT

GSK, Clover collaborate to assess protein-based coronavirus vaccine candidate



Treatments in Development

- Regeneron
- Gilead
- Takeda



Regeneron



- Hoping to have treatments ready for human testing by August

NEWS

Regeneron Might Have Coronavirus Treatment This Summer, Says CEO

Regeneron's CEO says his pharmaceutical company hopes to test a coronavirus treatment on humans by this Summer.



- Remdesivir
 - Remdesivir is an investigational nucleotide analog with broad-spectrum antiviral activity both in vitro and in vivo in animal models against multiple emerging viral pathogens including Ebola, Marburg, MERS and SARS.
 - two phase 3 studies are currently underway



Takeda



- Takeda Pharmaceutical is developing a new drug derived from the plasma of recovered COVID-19 patients
- When a person gets ill from a disease their body produces antibodies to combat the disease
- The idea is that plasma will be injected into current patients to help their bodies produce their own antibodies
- This type of treatment was used in helping to fight ebola



Additional Slides

Symptoms

Coronavirus

Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) are viral respiratory illnesses caused by a coronavirus.

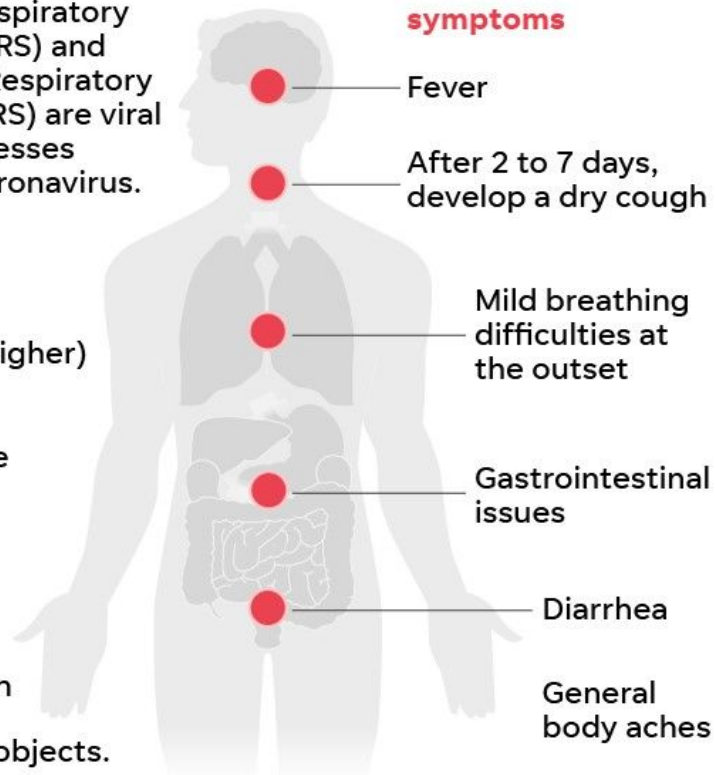
Severe symptoms

- High fever (100.4°F or higher)
- Pneumonia
- Kidney failure
- Death

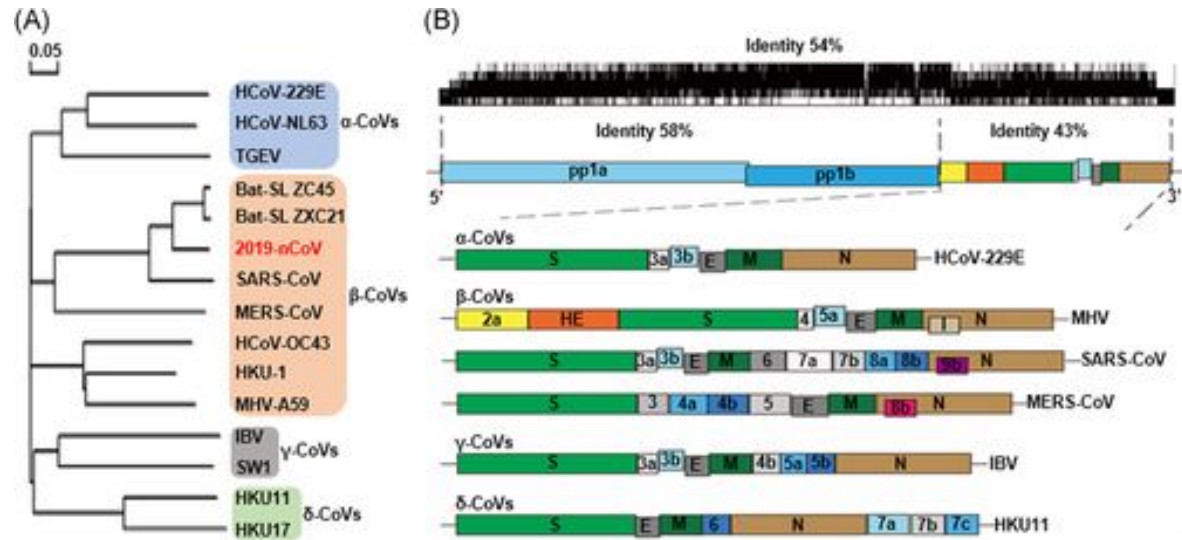
Transmission

Coughs or sneezes from infected person or touching contaminated objects.

Common symptoms



Genomics





Antigen and Hapten

- Antigen:
- Hapten:



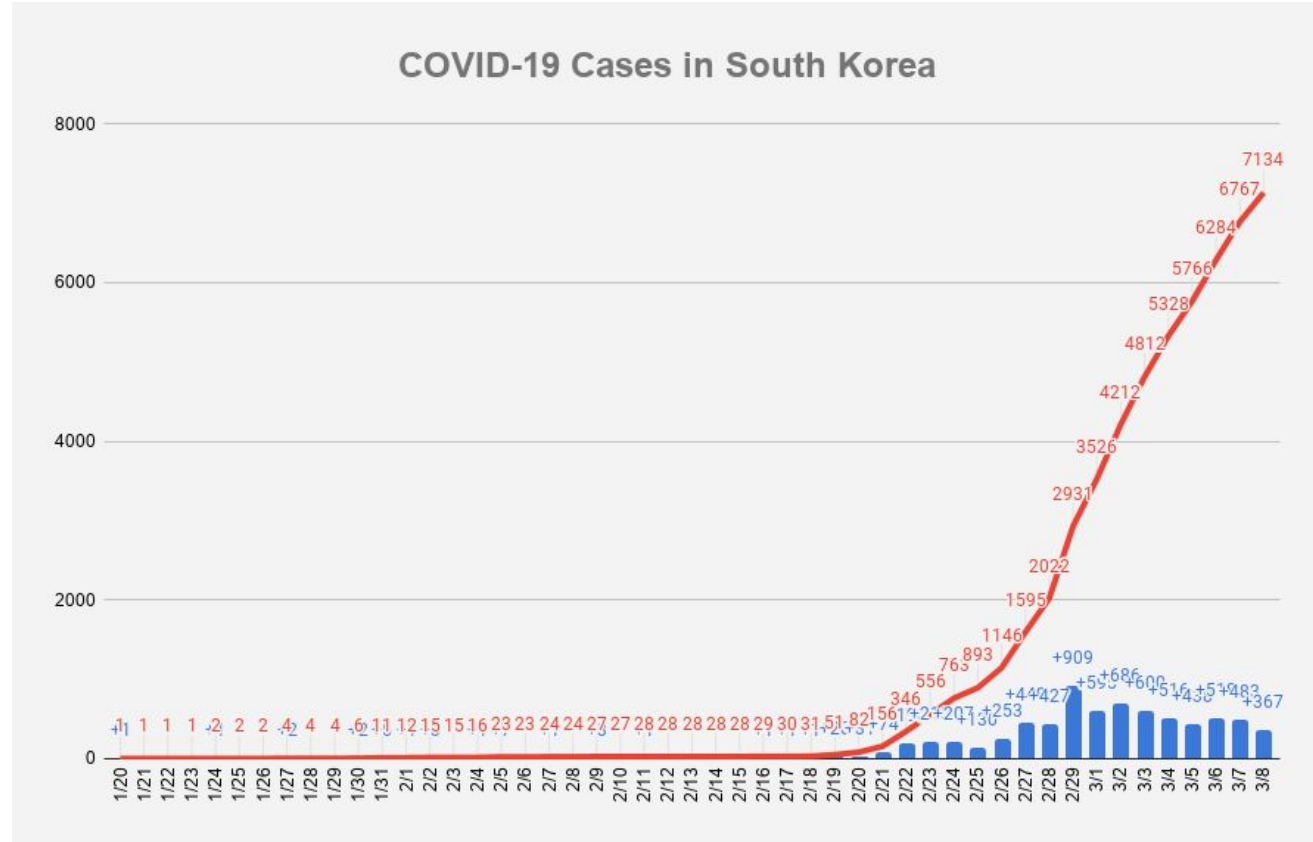
Antigenicity and Immunogenicity

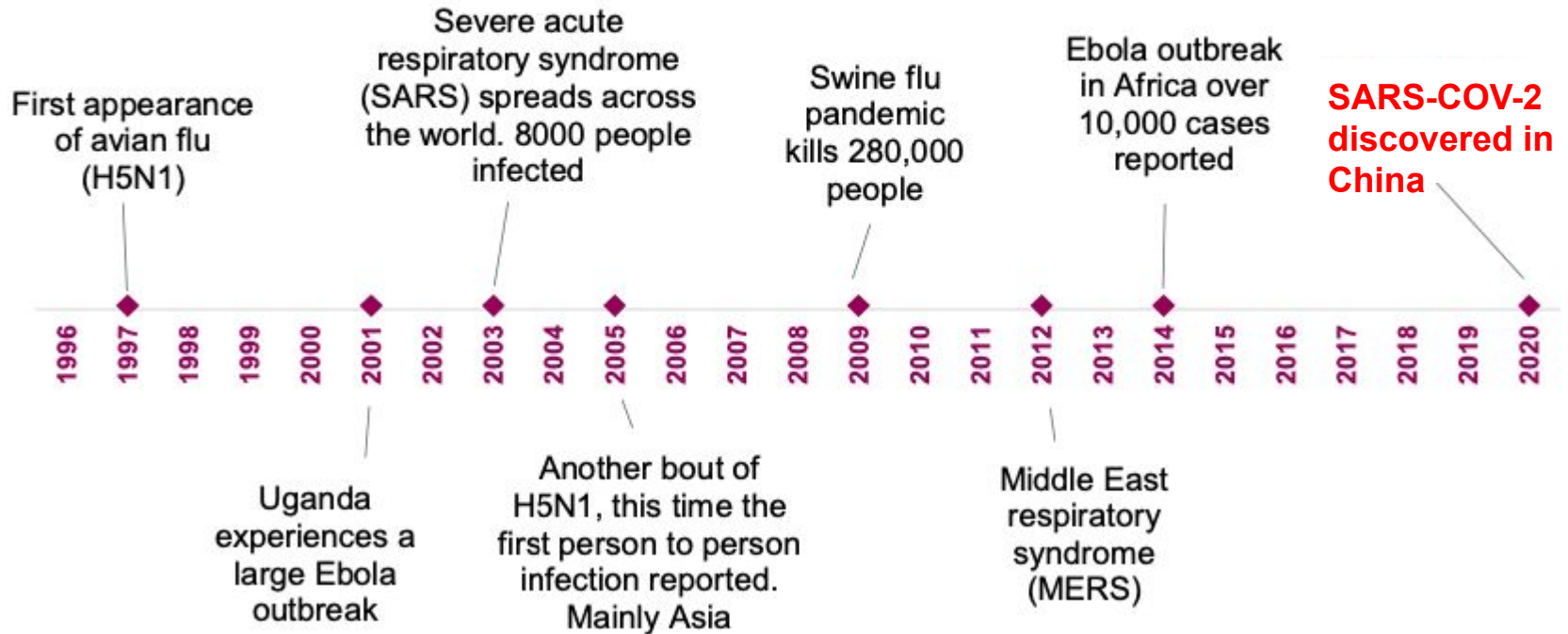
- Antigenicity: The capacity of a chemical structure (antigen) to bind to an antibody
- Immunogenicity: The capability of an antigen to induce an immune response

(note: in some older texts, antigenicity sometimes also refers to what today we term immunogenicity).

South Korea

Note the the number of new cases (in blue) are levelling off.





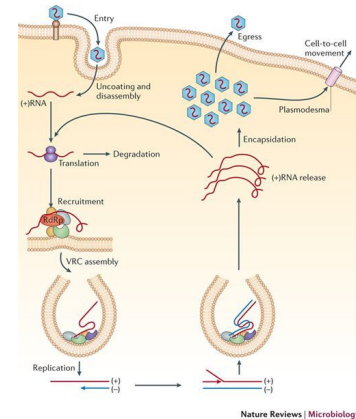


Recent Outbreaks

Outbreak	Virus type	Deaths
2003 severe acute respiratory syndrome outbreak	SARS-CoV	774 ^[31]
2012 Middle East respiratory syndrome coronavirus outbreak	MERS-CoV	Over 400 ^[32]
2015 Middle East respiratory syndrome outbreak in South Korea	MERS-CoV	36 ^[33]
2018 Middle East respiratory syndrome outbreak	MERS-CoV	41 ^[34]
2019–20 coronavirus outbreak	SARS-CoV-2	At least 3,286 ^[35]

(+)RNA virus infection cycle

Figure 1 | **Schematic infection cycle of positive-sense RNA viruses.** Positive-sense RNA ((+)RNA) viruses enter animal cells by endocytosis and plant cells through wounds. When the virus is inside the cell, the (+)RNA genome is released into the cytosol, where it is translated by the host ribosomes. The resulting viral replication proteins then recruit the (+)RNA to subcellular membrane compartments, where functional viral replication complexes (VRCs) are assembled. A small amount of negative-sense RNA ((-)RNA) is synthesized and serves as a template for the synthesis of a large number of (+)RNA progeny. The new (+)RNAs are released from the VRCs, whereas the (-)RNA is retained. The released (+)RNAs start a new cycle of translation and replication, become encapsidated, and then exit the cells (in the case of animal viruses) or move to neighbouring cells through plasmodesmata (in the case of plant viruses).





Comparing COVID-19 and Influenza Virus

R0:

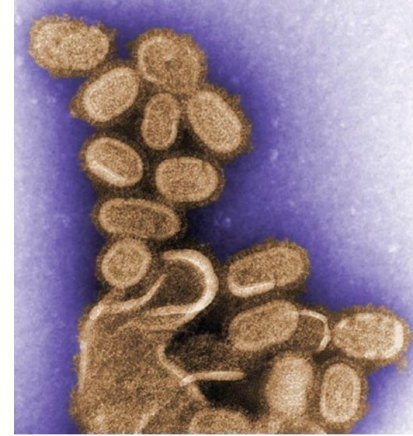
CFR:

1918 Pandemic (Spanish Flu)

500 million people globally infected - one-third of the global population

Mortality of 50 million; 675,000 in the US

Pandemic caused by strain of H1N1 virus - possibly of avian origin



A colorized image of the 1918 virus taken by a transmission electron microscope (TEM). The 1918 virus caused the deadliest flu pandemic in recorded human history, claiming the lives of an estimated 50 million people worldwide. Photo credit: C. Goldsmith - Public Health Image Library #11098.

SARS-like WIV1-CoV poised for human emergence

Vineet D. Menachery^a, Boyd L. Young Jr.^a, Amy C. Sims^a, Karl Debbs^{a,b}, Sudhakar S. Agnihothram^a, Lisa E. Gralinski^a, Rachel L. Graham^a, Tressa Schibye^a, Jessica A. Plant^a, Scott R. Royak^a, Jessica Swannstrom^a, Timothy P. Sheahan^a, Raymond J. Pickles^{a,c}, Davide Corti^{d,e}, Scott H. Randell^f, Antonio Lanzavecchia^g, Wayne A. Marasco^h, and Ralph S. Baric^{a,i,1}

^aDepartment of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599; ^bDepartment of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599; ^cDivision of Microbiology, National Center for Zoonotic Research, Food and Drug Administration, Jefferson, AL 37209; ^dDepartment of Cell Biology and Physiology and Marston Lung Institute, University of Illinois, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599; ^eInstitute for Research in Biomedicine, Bellinzona, Switzerland; ^fInstitute of Microbiology, Eidgenössische Technische Hochschule Zürich, Zurich, Switzerland; ^gMunich Medical Center, Berlin, Germany; ^hDepartment of Cancer Immunology and AIDS, Dana-Farber Cancer Institute-Department of Medicine, Harvard Medical School, Boston, MA 02215

Edited by Peter Palese, Icahn School of Medicine at Mount Sinai, New York, NY, and approved January 6, 2016 (received for review September 4, 2015)

Outbreaks from zoonotic sources represent a threat to both human disease as well as the global economy. Despite a wealth of metagenomics studies, methods to leverage these datasets to identify future threats are underdeveloped. In this study, we describe an approach that combines existing metagenomics data with reverse genetics to engineer reagents to evaluate emergence and pathogenic potential of circulating zoonotic viruses. Focusing on the severe acute respiratory syndrome (SARS)-like viruses, the study indicates that the WIV1-coronavirus (CoV) cluster has the ability to directly infect and may undergo limited transmission in human populations. However, in vivo attenuation suggests additional adaptation is required for epidemic disease. Importantly, available SARS monoclonal antibodies offered success in limiting viral infection absent from available vaccine approaches. Together, the data highlight the utility of a platform to identify and practice prophylactic strains harbored by animal reservoirs and document the threat posed by WIV1-CoV for emergence in human populations.

SARS | CoV | emergence | Spike | WIV1

Although previously associated with upper respiratory infections, the emergence of severe acute respiratory coronavirus (SARS-CoV) in 2002–2003, and more recently, Middle East respiratory syndrome (MERS)-CoV underscores the threat of cross-species transmission leading to violent pandemic viral infections (1, 2). Whereas prevailing research suggests that SARS-CoV emerged from viruses in the Chinese horseshoe bat, identifying a progenitor strain that used human angiotensin converting enzyme 2 (ACE2) had proven elusive (3, 4). However, recent metagenomics studies isolated several SARS-like virus sequences that share >90% genome-wide homology and represented the closest sequences to the epidemic strain (5, 6). Importantly, researchers also isolated replication competent virus WIV1-CoV, part of the Rd306 cluster, could use ACE2 orthologs and mediated low-level replication in human cells (5). Overall, the evidence indicates that SARS-CoV likely emerged from Chinese horseshoe bats and that similar viruses are still harbored in these populations.

The identification of WIV1-CoV and its capacity to use ACE2 orthologs offers a warning for possible reemergence and provides an opportunity to prepare for a future CoV outbreak. To achieve this goal, a new platform is required to translate metagenomics findings; the approach must generate critical diagnostic reagents, define emergence potential of novel strains, and determine efficacy of current therapeutics. Building on this premise, we developed a framework to examine circulating CoVs using reverse genetic systems to construct full-length and chimeric viruses. The results indicate that viruses using WIV1-CoV spike are poised to emerge in human populations due to efficient replication in primary human airway epithelial cell cultures. However, additional adaptation, potentially independent of the spike protein receptor-binding domain is required for pathogenesis and epidemic disease. Importantly, monoclonal antibody

strategies against SARS were effective against WIV1-CoV spike unlike available vaccine approaches. Together, the results highlight the utility of developing platforms to evaluate circulating zoonotic viruses as threats for future emergence and epidemic potential.

Results

The discovery of SARS-like virus clusters that bridge the gap between the epidemic strains and related precursor CoV strains (HKU1) virus provided the best evidence for emergence of SARS-CoV from Chinese horseshoe bats (5). Comparing the receptor binding domain (RBD), SARS-CoV (Urban) and WIV1 share homology at 11 of the 14 contact residues with human ACE2 (Fig. 1A); importantly, the three amino acid changes represent relatively conservative substitution not predicted to ablate binding (Fig. 1B). Therefore, exploring WIV1 strains allows examination of emergence, pathogenesis potential, and adaptation requirements. Using the SARS-CoV infection clone as a template (7), we designed and synthesized a full-length infectious clone of WIV1-CoV consisting of six plasmids that could be enzymatically cut, ligated together, and electroporated into cells to rescue replication competent progeny viruses (Fig. S1A). In addition to the full-length clone, we also produced WIV1-CoV

Significance

The emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) highlights the continued risk of cross-species transmission leading to epidemic disease. This manuscript describes efforts to extend surveillance beyond sequence analysis, constructing chimeric and full-length constructs to evaluate emergence potential. Focusing on SARS-like virus sequences isolated from Chinese horseshoe bats, the results indicate a significant threat posed by WIV1-CoV. Both full-length and chimeric, WIV1-CoV readily replicated efficiently in human airway cultures and in vivo, suggesting capability of direct transmission to humans. In addition, while monoclonal antibody treatments prove effective, the SARS-based vaccine approach failed to confer protection. Together, the study indicates an ongoing threat posed by WIV1-related viruses and the need for continued study and surveillance.

Author contributions: V.D.M., B.L.Y., and R.S.B. designed research; V.D.M., B.L.Y., A.C.S., R.L.G., L.E.G., T.P.S., J.A.P., S.H.R., J.S., and T.P.S. performed research; V.D.M., B.L.Y., R.J.P., D.C., S.H.R., and W.A.M. contributed new reagents/analytic tools; V.D.M., A.C.S., R.J.P., S.H.R., and R.S.B. analyzed data; and V.D.M. and R.S.B. wrote the paper.

The authors declare no conflict of interest.

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See Commentary on page 2812.

To whom correspondence should be addressed: Email: baric@med.unc.edu.

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A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence

Vincent D Menachery¹, Boyd I Yount Jr¹, Kari Debbink^{1,2}, Sudhakar Agnihothram³, Lisa E Gralinski¹, Jessica A Plante¹, Rachel I Graham¹, Trevor Scobey¹, Xing-Yi Ge⁴, Eric F Donaldson¹, Scott H Randell^{5,6}, Antonio Lanzavecchia⁷, Wayne A Marasco^{8,9}, Zheng-Li Shi⁴ & Ralph S Baric^{1,2}

The emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) underscores the threat of cross-species transmission events leading to outbreaks in humans. Here we examine the disease potential of a SARS-like virus, SHC014-CoV, which is currently circulating in Chinese horseshoe bat populations¹. Using the SARS-CoV reverse genetics system², we generated and characterized a chimeric virus expressing the spike of bat coronavirus SHC014 in a mouse-adapted SARS-CoV backbone. The results indicate that group 2b viruses encoding the SHC014 spike in a wild-type backbone can efficiently use multiple orthologs of the SARS receptor human angiotensin converting enzyme 2 (ACE2), replicate efficiently in primary human airway cells and achieve *in vitro* titers equivalent to epidemic strains of SARS-CoV. Additionally, *in vivo* experiments demonstrate replication of the chimeric virus in mouse lung with notable pathogenesis. Evaluation of available SARS-based immune-therapeutic and prophylactic modalities revealed poor efficacy; both monoclonal antibody and vaccine approaches failed to neutralize and protect from infection with CoVs using the novel spike proteins. On the basis of these findings, we synthetically re-derived an infectious full-length SHC014 recombinant virus and demonstrate robust viral replication both *in vitro* and *in vivo*. Our work suggests a potential risk of SARS-CoV re-emergence from viruses currently circulating in bat populations.

The emergence of SARS-CoV heralded a new era in the cross-species transmission of severe respiratory illness with globalization leading to rapid spread around the world and massive economic impact^{3,4}. Since then, several strains—including influenza A strains H5N1, H1N1 and H7N9 and MERS-CoV—have emerged from animal populations, causing considerable disease, mortality and economic hardship for

the afflicted regions⁵. Although public health measures were able to stop the SARS-CoV outbreak⁶, recent metagenomics studies have identified sequences of closely related SARS-like viruses circulating in Chinese bat populations that may pose a future threat^{1,4}. However, sequence data alone provides minimal insights to identify and prepare for future pre-pandemic viruses. Therefore, to examine the emergence potential (that is, the potential to infect humans) of circulating bat CoVs, we built a chimeric virus encoding a novel, zoonotic CoV spike protein—from the RdSHC014-CoV sequence that was isolated from Chinese horseshoe bats¹—in the context of the SARS-CoV mouse-adapted backbone. The hybrid virus allowed us to evaluate the ability of the novel spike proteins to cause disease independently of other necessary adaptive mutations in its natural backbone. Using this approach, we characterized CoV infection mediated by the SHC014 spike protein in primary human airway cells and *in vivo*, and tested the efficacy of available immune therapeutics against SHC014-CoV. Together, the strategy translates metagenomics data to help predict and prepare for future emergent viruses.

The sequences of SHC014 and the related RaTWT1-CoV show that these CoVs are the closest relatives to the epidemic SARS-CoV strains (Fig. 1a,b); however, there are important differences in the 14 residues that bind human ACE2, the receptor for SARS-CoV, including the five that are critical for host range: Y442, L472, N479, T487 and Y491 (ref. 7). In WTV1, three of these residues vary from the epidemic SARS-CoV Urbani strain, but they were not expected to alter binding to ACE2 (Supplementary Fig. 1a,b and Supplementary Table 1). This fact is confirmed by both pseudotyping experiments that measured the ability of lentiviruses encoding WTV1 spike proteins to enter cells expressing human ACE2 (Supplementary Fig. 1) and by *in vitro* replication assays of WTV1-CoV (ref. 1). In contrast, 7 of 14 ACE2-interaction residues in SHC014 are different from those in SARS-CoV, including all five residues critical for host range (Supplementary Fig. 1c and Supplementary Table 1). These changes, coupled with

¹Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. ²Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. ³National Center for Toxicological Research, Food and Drug Administration, Jefferson, Arkansas, USA. ⁴Key Laboratory of Special Pathogens and Biosafety, Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan, China. ⁵Department of Cell Biology and Physiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. ⁶Cities of North Carolina, Marion Long Institute, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. ⁷Institute for Research in Biomedicine, Bellinzona Institute of Microbiology, Zurich, Switzerland. ⁸Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA. ⁹Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA. Correspondence should be addressed to R.S.B. (rsbaric@med.unc.edu) or Z.L.S. (zshil@med.unc.edu).

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